EPIDEMIOLOGY

The autoantibody rheumatoid factor may be an independent risk factor for ischaemic heart disease in men

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Background: Subjects with rheumatoid arthritis have an increased prevalence of ischaemic heart disease (IHD). This is most likely in those people with the autoantibody rheumatoid factor (RF). RF is strongly associated with rheumatoid arthritis (RA) but is also present in up to 15% of all adults.
Objective: To determine whether RF might identify people in a general population who also share an increased likelihood of developing IHD.
Methods: Subjects from the Hertfordshire Cohort Study were investigated for the presence of RF. Subjects completed a questionnaire and attended a clinic where a history of IHD was recorded (ECG, coronary artery bypass grafting, Rose chest pain). Associations between the presence of RF, antinuclear antibodies (ANA), anticardiolipin antibodies (ACA) and IHD in 567 men and 589 women were investigated and compared with traditional risk factors for IHD.
Results: RF was associated with an increased likelihood of IHD in men (odds ratio (OR) = 3.1, 95% CI 1.7 to 5.4, $p<0.001$). This increased risk could not be explained by traditional risk factors for IHD (mutually adjusted OR for RF 2.9 (95% CI 1.6 to 5.3), $p<0.001$). There was no significant association between RF in women or between ANA or ACA with IHD in men or women.
Conclusion: This work suggests that RF is an independent risk factor for IHD in the general population. It lends support to the importance of inflammation in atherosclerosis and suggests that autoimmune processes may be involved. In addition, it raises the intriguing possibility that RF may have a direct role in the pathogenesis of IHD in some subjects.

Ischaemic heart disease (IHD) is a leading cause of death in the Western world. Most subjects with IHD have one or more traditional risk factors, including diabetes, a smoking history, hypertension, obesity, a family history of IHD or hyperlipidaemia.[1] In recent years new risk factors for IHD have been identified, including the presence of inflammation as demonstrated by a raised highly sensitive C reactive protein (hs-CRP).[2] Subjects with chronic inflammatory diseases such as rheumatoid arthritis (RA) and systemic lupus erythematosus also have a greatly increased risk of developing IHD.[3]

The autoantibody rheumatoid factor (RF) is strongly associated with RA, may be present in subjects many years before they develop RA[4] and its presence confers a risk of developing RA that increases with increasing titre.[5] However, RF is associated with other autoimmune rheumatic diseases, viral or bacterial infections and is present in as many as 15% of normal adults.[6] Recently, RF has been associated with an increased likelihood of developing IHD in patients with inflammatory polyarthritis.[7]

We hypothesised that the presence of RF in a general population may identify subjects with a similar immune pathology to patients with RA, who may also share an increased likelihood of developing IHD, and that RF may have a special role in the pathogenesis of IHD. To explore this we investigated whether the presence of RF was associated with an increased risk of IHD among a population of elderly men and women in the Hertfordshire Cohort Study (HCS). We also studied other common autoantibodies, antinuclear antibodies (ANA) and anticardiolipin antibodies (ACA), to see if any effect observed was specific to RF or due to non-specific polyclonal B-cell expansion.

PATIENTS AND METHODS

The HCS methods have been described previously.[8] The HCS population has been shown to be representative of the rest of the population of England. This has been determined by comparing the HCS with information from the nationally representative Health Survey for England.[9]

In brief, 737 men and 675 women born in Hertfordshire between 1931 and 1939 and still living in East Hertfordshire in 1998 attended a home interview and clinic where information on their medical and social history, including the presence of IHD and traditional cardiovascular risk factors, was collected. The selection procedure for these subjects was as follows: with the help of the National Health Service Central Registry at Southport and the Hertfordshire Family Health Service Association, we traced men and women who were born between 1931 and 1939 in Hertfordshire, and still lived there during the period 1998–2003. The birth weight and weight at 1 year of age of each person had been recorded in a ledger by a team of midwives and health visitors who had attended each birth in Hertfordshire in the 1930s and visited the child's home at intervals during the first year of life. After obtaining written permission from each subject's general practitioner, we approached each person by letter, asking them if they would be willing to be contacted by one of our research nurses. If they agreed, a research nurse performed a home visit, where they

Abbreviations: ACA, anticardiolipin antibodies; ANA, antinuclear antibodies; BMI, body mass index; CABG, coronary artery bypass grafting; HCS, Hertfordshire Cohort Study; HDL, high-density lipoprotein; HRT, hormone replacement therapy; hs-CRP, highly sensitive C reactive protein; IHD, ischaemic heart disease; LDL, low-density lipoprotein; RA, rheumatoid arthritis; RF, rheumatoid factor

Table 1 Subjects' characteristics

Frequency (%)	Men (n = 567)	Women (n = 589)
Ischaemic heart disease	66 (11.6)	54 (9.2)
Rheumatoid factor positive	92 (16.2)	73 (12.4)
ANA positive (Inova or Axis-Shield, or both)	61 (10.8)	72 (12.2)
ACA positive (top octile of IgG or IgM)	137 (24.2)	116 (19.7)
Ex-smoker	297 (52.4)	168 (28.5)
Current smoker	94 (16.6)	61 (10.4)
Family history of myocardial infarction*	236 (41.6)	293 (49.7)
Previously or newly diagnosed diabetes	39 (6.9)	43 (7.3)
High blood pressure (≥160/100 mm Hg or medication)	193 (34.0)	228 (38.7)
BMI (kg/m^2), mean (SD)	26.9 (3.7)	27.3 (4.9)
Total fasting cholesterol (mmol/l), mean (SD)	5.9 (1.0)	6.6 (1.2)
Ratio of total to HDL cholesterol†	4.5 (1.3)	3.9 (1.3)

ACA, anticardiolipin antibodies; ANA, antinuclear antibodies; BMI, body mass index; HDL, high-density lipoprotein.
*Premature myocardial infarction in a first-degree relative (before age 55 years in men, before age 65 years in women).
†Geometric mean and SD.

administered a structured questionnaire. This included information on socioeconomic status, medical history, cigarette smoking, alcohol consumption, dietary calcium intake and reproductive variables in women. Physical activity was assessed by a previously validated questionnaire.[7]

Prevalent IHD was identified by a history of typical angina according to the Rose chest pain questionnaire, previous coronary artery bypass grafting (CABG) or angioplasty, or the presence of pathological Q waves on an ECG. The ECG was read by a trained physician with extensive experience of similar studies using the Minnesota code.[10] This method has been well validated in a number of studies.[11] Information on traditional risk factors for IHD included family history (history of premature myocardial infarction in a first-degree relative (before the age of 55 in men, before the age of 65 in women)), lipid profile, body mass index (BMI), hypertension (using antihypertensive drugs or systolic blood pressure ≥160 mm Hg and/or diastolic blood pressure ≥100 mm Hg—based on the British Hypertension Society definition of high blood pressure requiring treatment and WHO definition of moderate hypertension[12]), smoking (current, previous, never and an estimate of pack-years) and diabetes (previously known or newly diagnosed according to the WHO oral glucose tolerance test 2 hour criteria—that is, ≥11.1 mmol/l)).

Subjects attended the morning clinics fasting. At this visit, a glucose tolerance test was performed using 75 g anhydrous glucose, with blood samples obtained at baseline, 30 minutes and 120 minutes. Fasting samples were analysed for measurement of total cholesterol, high-density lipoprotein (HDL) cholesterol, triglycerides, apolipoprotein(a) and (b). Low-density lipoprotein (LDL) cholesterol concentrations were calculated using the Friedwald–Fredrickson method. A resting 12-lead ECG was obtained and coded for presence of pathological Q waves by one trained observer. Sitting blood pressure was measured. Height was measured to the nearest 0.1 cm using a Harpenden pocket stadiometer (Chasmors Ltd, London, UK) and weight to the nearest 0.1 kg on a SECA floor scale (Chasmors Ltd, London, UK). BMI was calculated as weight divided by height squared (kg/m^2).

A serum sample was taken and ELISAs used to measure RF (Inova Diagnostics, San Diego, USA), ANA (Inova Diagnostics and Axis-Shield plc, Dundee, UK) and ACA IgM or IgG, or both (ORGENTEC Diagnostika, Mainz, Germany). Positive results were defined by the manufacturer's instructions (RF ≥6 IU/ml, ANA >6 U/ml (Inova) and >1 U/ml (Axis-Shield), ACA IgM >7 U/ml and ACA IgG >10 U/ml).

We used logistic regression models to investigate associations between the presence of RF, ANA, ACA and traditional IHD risk factors and prevalent IHD. Known risk factors for IHD were considered as potential confounding factors and included in the mutually adjusted model with RF, ANA or ACA as predictors of IHD. Mutually adjusted analyses included all risk factors being incorporated simultaneously in a model with RF, ANA or ACA as predictors of IHD. Analyses were restricted to the 567 men and 589 women with data available for IHD, RF, ANA and ACA and all of the traditional risk factors of interest. The study had ethical approval from the local research ethics committee and all subjects gave written informed consent.

Table 2 IHD in relation to RF and traditional IHD risk factors among 567 men and 589 women from the Hertfordshire Cohort Study

	Men (n = 567)			Women (n = 589)		
	IHD +ve No (%)	Unadjusted OR (95% CI)	Mutually adjusted OR (95% CI)	IHD +ve No (%)	Unadjusted OR (95% CI)	Mutually adjusted OR (95% CI)
RF positive (≥6 IU/ml vs <6 IU/ml)	22 (23.9)	3.1 (1.7 to 5.4)	2.9 (1.6 to 5.3)	8 (11.0)	1.3 (0.6 to 2.8)	1.3 (0.6 to 2.8)
Ex-smoker vs never smoker	39 (13.1)	1.3 (0.7 to 2.4)	1.2 (0.6 to 2.2)	16 (9.5)	1.1 (0.6 to 2.0)	1.0 (0.5 to 1.9)
Current smoker vs never smoker	9 (9.6)	0.9 (0.4 to 2.2)	1.0 (0.4 to 2.3)	6 (9.8)	1.1 (0.4 to 2.8)	1.1 (0.4 to 2.9)
Family history of myocardial infarction* (yes vs no)	13 (19.7)	2.1 (1.1 to 4.1)	1.9 (0.9 to 3.9)	13 (12.3)	1.5 (0.8 to 2.9)	1.3 (0.7 to 2.6)
Previously/newly diagnosed diabetes (yes vs no)	9 (23.1)	2.5 (1.1 to 5.5)	1.7 (0.7 to 4.1)	6 (14.0)	1.7 (0.7 to 4.2)	1.2 (0.4 to 3.1)
High blood pressure (yes vs no)	43 (22.3)	4.4 (2.5 to 7.5)	3.9 (2.2 to 6.8)	32 (14.0)	2.5 (1.4 to 4.5)	2.3 (1.2 to 4.1)
BMI (z score increase)	–	1.1 (0.9 to 1.5)	1.0 (0.7 to 1.3)	–	1.3 (1.0 to 1.7)	1.2 (0.9 to 1.6)
Total fasting cholesterol (z score increase)	–	0.8 (0.6 to 1.1)	–	–	0.8 (0.6 to 1.1)	–
Total cholesterol:HDL ratio (z score decrease)	–	1.1 (0.9 to 1.5)	1.1 (0.8 to 1. 5)	–	1.1 (0.8 to 1.4)	1.0 (0.8 to 1.4)

BMI, body mass index; HDL, high-density lipoprotein; IHD, ischaemic heart disease; OR, odds ratio; RF, rheumatoid factor.
Total cholesterol and HDL:LDL ratio were correlated; HDL:LDL ratio was included in mutually adjusted models.
*Premature myocardial infarction in a first-degree relative (before age 55 years in men, before age 65 years in women).

Table 3 Prevalence of IHD according to ANA, ACA and RF positivity, together with unadjusted and adjusted odds ratios for IHD

	Men (n = 567)			Women (n = 589)		
Antibody status	n	No (%) with IHD	OR for IHD (95%CI)	n	No (%) with IHD	OR for IHD (95%CI)
ACA*						
−ve	430	51 (11.9)	–	473	41 (8.7)	–
+ve	137	15 (10.9)	0.9 (0.5 to1.7), p = 0.77 1.1 (0.6 to 2.0), p = 0.81†	116	13 (11.2)	1.3 (0.7 to 2.6), p = 0.40 1.3 (0.7 to 2.6), p = 0.41†
ANA						
−ve	506	62 (12.3)	–	517	50 (9.7)	–
+ve	61	4 (6.6)	0.5 (0.2 to1.4), p = 0.20 0.5 (0.2 to1.6), p = 0.25†	72	4 (5.6)	0.6 (0.2 to1.6), p = 0.26 0.6 (0.2 to1.6), p = 0.28†
RF						
−ve	475	44 (9.3)	–	516	46 (8.9)	–
+ve	92	22 (23.9)	3.1 (1.7 to 5.4), p<0.001 2.9 (1.6 to 5.3), p<0.001†	73	8 (11.0)	1.3 (0.6 to 2.8), p = 0.57 1.2 (0.5 to 2.8), p = 0.61†

ACA, anticardiolipin antibodies; ANA, antinuclear antibodies; IHD, ischaemic heart disease; OR, odds ratio; RF, rheumatoid factor.
*ACA positivity defined as the top octile from the IgG or IgM ELISA.
†Odds ratio adjusted for BMI, smoking status, family history of IHD, diabetes, high blood pressure and HDL:LDL ratio.

RESULTS

The subjects were aged between 59 and 71 years. The age range was 12 years, although the date of birth range was 8 years, because the study was carried out over 4 years. The prevalence of IHD was 11.6% in men and 9.2% in women (table 1). In men and women a number of traditional risk factors were associated with an increased likelihood of having IHD (table 2). A positive RF was present in 92 (16.2%) men and 73 (12.4%) women.

In men, RF as defined by an ELISA, was associated with an increased likelihood of having IHD (table 2) with an unadjusted odds ratio of 3.1 (95% CI 1.7 to 5.4), p<0.001. This increased risk of IHD could not be explained by its traditional risk factors—that is, family history, smoking, diabetes mellitus, hypertension, body mass index and cholesterol (table 2, mutually adjusted odds ratio for RF in men 2.9 (95% CI 1.6 to 5.3), p<0.001). The analysis in the paper was adjusted for smoking by comparing current smokers with those who had never smoked, and ex-smokers with those who had never smoked. Adjusting by pack-years made little difference to the overall odds ratios and statistical significance. We also explored the relationship between IHD and RF titre with RF positivity categorised as negative, low positive (less than median) and high positive (greater than median). However, the odds ratios were comparable for the low positive and the high positive compared with the negatives (ORs of 3.2 (95% CI 1.5 to 6.7), p = 0.002 for low positives, and 3.0 (95% CI 1.4 to 6.3), p = 0.004 for the high positives). In addition, analysis done using a cut-off point of 30 IU/ml still showed a significant association between RF and IHD and no dose–response.

There was no significant association between RF and IHD in women with an unadjusted odds ratio of 1.3 (95% CI 0.6 to 2.8), p = 0.57 (table 2). This was unchanged if hormone replacement therapy (HRT) was taken into account. Of 589 women, 56.7% had never used HRT, 18.3% had not used HRT for 5 years, 7.5% had used HRT in the past 5 years and 17.5% were current HRT users.

We also analysed the men and women together. The odds ratios for RF positive and high blood pressure changed a little (went down compared with the original analysis for men and went up for women). The result still showed a significant increase in the presence of IHD in RF positive subjects. The odds ratios for the other factors remained much the same.

The original analyses for men and women were repeated using the RF latex results instead of the ELISA results to define RF positivity. The odds ratios for RF and IHD did not change significantly. In addition, 14 subjects with RA were identified in the cohort. Reanalysing the work after removal of these 14 subjects did not significantly alter the result.

A positive test for ANA (defined as being positive according to the manufacturer's instructions for the Axis-Shield or Inova assays, or both) was present in 61 (10.8%) men and 72 (12.2%) women. A positive test for ACA (for IgG or IgM, or both, according to the manufacturer's instructions) was present in 18 (3%) men and 12 (2%) women. There were no associations between a positive ANA and IHD in men or women (table 3). The low prevalence of ACA positivity using the manufacturer's instructions made further analysis impossible. To attempt to overcome this we investigated associations between IHD and a positive ACA defined firstly as IgM and/or IgG within the top fifth of the distribution from the ELISA (prevalence of 37% for men and 30% for women), and secondly as IgM and/or IgG within the top octile of the distribution from the ELISA (prevalence of 24.2% for men and 19.7% for women). There were no associations between a positive ACA using either of the above definitions and IHD in men or women (table 3 presents results for the octile definition).

DISCUSSION

Our results appear to show an association between the autoantibody RF and an increased risk of IHD in men from a general population. This was independent of traditional risk factors, and the magnitude of association was similar to that for diabetes and hypertension in this study. RFs are present in up to 15% of elderly subjects[6] and may arise through polyclonal B-cell activation such as that caused by infectious organisms or by antigen-driven proliferation of B cells associated with autoimmune diseases, including RA.[13] Although RF is strongly associated with RA and RA is associated with increased cardiovascular morbidity and mortality,[3] the increased risk in our study is unlikely to be due to active RA or its treatment. The prevalence of RA in men in the United Kingdom is estimated to be 0.4%,[14] making it unlikely that our cohort contains many men with RA. In addition, we investigated all subjects with a positive RF (RF >30 IU/ml) by asking them to attend a clinic where a consultant rheumatologist assessed them for a diagnosis of RA and looked for a general practitioner recorded diagnosis of RA in their records. This identified 10 women and four men with RA and their removal from the analysis did not alter the result.

A higher RF titre than the 6 IU/ml we selected is normally used in the diagnosis of RA. In this study we were not looking at the association between IHD and RA but at the association

between RF and IHD. With this in mind we used the lower limit of accurate detection in the ELISA system (6 IU/ml). Analysis done using a cut-off point of 30 IU/ml still showed a significant association between RF and IHD.

The HCS population has been shown to be representative of the population of England using a number of measures, including the prevalence of IHD.[9] The study population showed strong associations between a number of traditional risk factors for IHD, including hypertension, diabetes and a positive family history of myocardial infarction. However, the size of the effects for smoking status was smaller than expected and there was no effect of hypercholesterolaemia or total:HDL cholesterol ratio. This may reflect modification of lifestyle in response to the diagnosis of IHD and reflects the difficulties of studying a relationship between IHD and a risk factor in a cross-sectional rather than a longitudinal study. People with a history of IHD may already have started to receive cholesterol-lowering treatment and, together with subjects with a smoking history, have made lifestyle adjustments. In addition, 9% of all subjects in this study sample were taking a statin or fibrate. Further analysis showed that excluding statin and fibrate users disclosed a stronger association between hypercholesterolaemia and IHD in men but not women. The OR for IHD in men for each SD decrease in total:HDL cholesterol ratio if statin and fibrate users were excluded was 1.52 (95% CI 1.07 to 2.17 $p = 0.02$). Men who were RF positive had a slightly higher measured systolic blood pressure than those who were RF negative (mean (SD), 140.4 (20.1) mm Hg vs 136.3 (18.3) mm Hg, $p = 0.05$ unadjusted, and $p = 0.03$ when adjusted for age, BMI, current social class, smoking and alcohol). There was no relationship for diastolic blood pressure in men, or for systolic or diastolic pressure in women. There was no difference in the prevalence of newly diagnosed diabetes mellitus or impaired glucose tolerance according to RF status in men or women.

Recently, inflammation measured by hs-CRP was identified as a risk factor for IHD.[2] IHD is most often due to atherosclerotic coronary artery disease. The importance of inflammation in atherosclerosis is also supported by the finding of inflammatory cells in atherosclerotic lesions.[15] The association of RF with IHD provides further evidence of the importance of inflammation and raises the possibility that autoimmune mechanisms may play a part. Our study cannot determine whether RF in the subjects examined is a non-specific marker of inflammation or is involved directly in the pathogenesis of atherosclerosis. However, RF appears to cause direct tissue damage in RA as a constituent of immune complexes,[13] perhaps by activating complement. It might cause damage to the endothelium in a similar way. There is circumstantial evidence for this: atherosclerotic plaques contain immunoglobulins and complement suggesting immune complex activity.[15] In addition, the lack of a relationship between IHD and the autoantibodies ANA and ACA suggests that the association between RF and IHD was not due to non-specific polyclonal B-cell activation secondary to inflammation but that RF may have a unique role in the pathogenesis of IHD/atherosclerosis. This is further supported by the association of RF with IHD in subjects with inflammatory arthritis.[7] There is also an intriguing possibility that the pathological process involved in IHD, such as atheroma formation, may generate inflammatory tissue capable of producing RF. However, these interesting questions cannot be answered in a cross-sectional study.

Might RF be just a marker of other underlying causes of IHD? Infections cause inflammation and can induce RF production, although this is usually short lived. Chronic infections that induce persistent RF are rare in the UK. Acute infections are associated with an increased risk of cardiovascular events, perhaps by inducing circulating cytokines or an autoimmune response.[16] Increased numbers of infectious episodes or ''pathogen burden'' has been associated with increased hs-CRP.[17] We plan to measure hs-CRP in our study cohort to determine the relationship between RF, IHD and inflammation. In addition, RF positive men were almost twice as likely to be current or ex-smokers than RF positive women (73% vs 38%). Smoking has been shown to be an environmental risk factor for the development of seropositive RA.[18] Might the presence of RF in our study population just be a marker of a previous or current smoking history? This does not appear to be the case as adjusting our results for smoking history along with other traditional risk factors produced little change in the association between RF and IHD.

This study has a number of potential limitations. The most important is the fact that this is a cross-sectional study and will therefore need confirmation in a longitudinal cohort study. Cross-sectional studies in an elderly population are always potentially susceptible to survival bias. However, in our study this would tend to bias the results towards the null hypothesis and is therefore unlikely to explain the findings.

This study may also be susceptible to ascertainment bias in that it may underestimate the number of subjects with IHD. As the study population was aged 59–71 years some subjects with IHD might have died before the study took place. It is also unclear why this effect should be seen in men but not in women. However, this may be owing to the selection of different populations from men and women in the study. The presence of IHD was defined on the basis of a history of angina, CABG/angioplasty or pathological Q waves on ECG. Seventy-two per cent of the men defined as having IHD had a history of CABG/angioplasty or had Q waves on an ECG. This is in contrast to the women, whose definition of IHD was less certain, being based on a history of angina alone in 60% of cases. We have analysed the data including only women with a definition of IHD based on a history of CABG/angioplasty or with pathological Q waves on ECG. This showed an increase in the association between RF and IHD in women (unadjusted OR = 1.6 (95% CI 0.5 to 4.9), $p = 0.41$; adjusted OR = 1.5 (95% CI 0.5 to 4.7), $p = 0.45$), although the relationship was still not statistically significant at the 5% level owing to the small number of cases of IHD ($n = 22$) among women according to this definition. In addition, it is possible that RF is associated with classical atherosclerotic disease, more commonly seen in men, rather than small vessel disease, more commonly seen in women.

This work suggests that RF is an independent risk factor for IHD in men from a general population. It lends support to the importance of inflammation in atherosclerosis and suggests that autoimmune processes may play a part. In addition, it raises the intriguing possibility that RF may have a direct role in the pathogenesis of some subjects with IHD.

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IMAGES IN CARDIOLOGY

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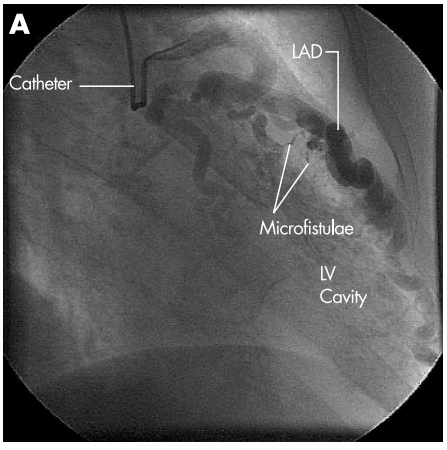
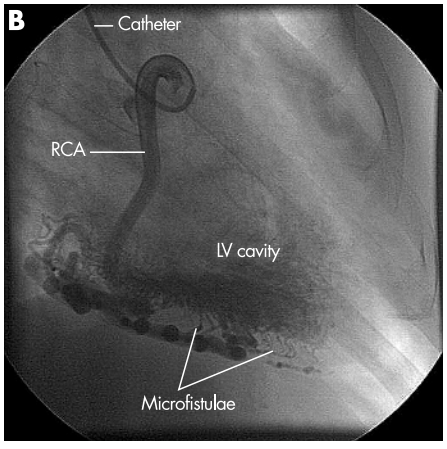
Multiple coronary artery fistulae or Thebesian veins?

A previously healthy 55-year-old patient presented with progressive exertional chest pain. Physical examination showed no abnormalities except for a diastolic cardiac murmur. The ECG showed left ventricular hypertrophy. The laboratory findings and the chest *x* ray were normal.

An exercise treadmill test was positive. The echocardiogram showed multiple diastolic jets draining into the left ventricle. A coronary artery angiogram disclosed strongly dilated left and right coronary arteries with multiple microfistulae draining into the left ventricle (panels A and B). In our patient besides the diagnosis of microfistulae, a diagnosis of persistent venae cordis minimae (Thebesian veins) was also considered. However, because there were direct connections between the coronary arteries and visible small vessels draining into the left ventricle and because both coronary arteries showed tortuosity and were strongly dilated (flow-mediated dilatation), we believed that this was a case of multiple fistulae rather than persistent Thebesian veins.





Coronary artery fistulae have an incidence of 0.2% in patients undergoing diagnostic cardiac catheterisation. The normal sites of origin are the right coronary artery (55–60%), the left coronary artery (35%), and both coronary arteries (5%). The most common sites of termination are the right ventricle (40%) and right atrium (23%). Sporadically, coronary artery fistulae drain into the left ventricle. The definitive treatment for coronary artery fistulae is surgery or transcatheter embolisation, but given the anatomy, our patient is currently being evaluated for heart transplantation.

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