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Repeat Coronary Angiography with Previously Normal Arteries: A Futile Exercise?

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Objectives: Up to 20% of coronary angiograms reveal normal arteries. How long they stay normal is poorly understood. This study investigated the fate of normal coronary arteries and determined the rate of development of coronary artery disease. Methods: We interrogated the angiographic archive of the South Yorkshire Cardiothoracic Centre between 2004 and 2013 to identify patients with truly normal coronary arteries who underwent repeat coronary angiography more than 1 year later. Follow up angiograms were scored for the severity and extent of CAD (graded per segment as 0%, 1–50%, >50%). Risk factors for the development of coronary artery disease were documented. Univariate predictors of disease development were identified and entered into a logistic regression model to identify independent predictors. Results: Out of over 25,000 angiographic procedures in the archives we found 6068 patients reported to have normal coronary arteries. Of these, 162 patients had also undergone subsequent repeat coronary angiography. Of these, 97 had truly normal (smooth) coronary arteries at baseline and had undergone repeat angiography >1 year later. At a median 51 months, 87 continued to have normal arteries, and all the remaining 10 had mild disease only (average 37% stenosis in an average 1.2 segments). No patients developed any significant (>50% stenosis) disease. Advanced age, time between angiograms, and smoking status were identified as independent predictors of development of CAD. Conclusions: Truly normal coronary arteries do not progress to significant disease within a time frame of 4 years. Repeat coronary angiography within that period is probably not indicated.

Key words: angiography; coronary artery disease; normal coronary arteries

INTRODUCTION

In 2012, 241,240 coronary angiograms were performed in the UK [1]. Up to 20% of all coronary angiograms reveal normal arteries [2,3]. This figure can be as high as 72% in patients presenting with 'atypical' chest pain [3]. The natural history of normal coronary arteries and, importantly, how long they stay normal, is poorly understood.

The American Heart Association has issued guidelines on the indications for coronary angiography [4]. But the impact of a prior normal coronary angiogram upon future decision making is not discussed. This, together with a lack of data on atherosclerotic disease development in later life, leads to a tendency among cardiologists to subject these patients, when they re-present, to repeat procedures that are both costly and not without risk.

The most common indication for coronary angiography is the investigation of symptoms consistent with ischemic heart disease. As many as 42% of patients investigated for stable angina have a normal coronary angiogram, suggesting that there are opportunities to improve patient selection [5]. In addition, cardiac surgery in patients with valvular disease usually requires coronary angiography to be performed as part of pre-

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operative assessment, although there are no large clinical trials that prove its value, and many of these disclose normal arteries. Guidelines recommend coronary angiography before surgery only in symptomatic or elderly patients with multiple risk factors [6]. The guidelines do not specify an appropriate maximum time frame between angiography and surgery, because of the lack of certainty from the limited literature concerning the duration of normality. A lack of evidence in this area frequently results in repeat angiography and delayed surgery.

The aim of this study was to determine the fate of truly normal coronary arteries in the 'real world' and attempt to elicit any potential predictors of disease development.

METHODS

Study Population

This was a retrospective analysis of a prospectively kept database of all patients undergoing coronary angiography at the South Yorkshire Cardiothoracic Centre (SYCC) between 2004 and 2013. The SYCC is the regional cardiothoracic centre, with a catchment population of 1.8 million, at which are performed approximately 2,500 coronary angiograms, 1,600 percutaneous coronary interventions (PCIs), and 800 open heart operations per year.

Data Collection

In the study period, there were >25,000 coronary angiographic procedures recorded on the database. All patients recorded by the operator as having a "normal" coronary angiogram were identified. From this number we identified all those that had undergone repeat angiography more than 1 year later. The original coronary angiograms were reviewed by a single experienced interventional Cardiologist (JG) to identify those with truly normal arteries (i.e., those with an entirely smooth lumen). Patients with any evidence of atherosclerosis at baseline were excluded. Repeat angiograms were analyzed and scored according to disease severity and location. Quantitative coronary angiography (QCA) was performed on any segments of artery identified as being diseased (Philips, Eindhoven). A stenosis of greater than 50% diameter in two views or greater than 70% in one view were considered significant. The extent of disease was scored according to the number of main epicardial coronary artery segments involved. The segments were 3–4 in the right coronary artery, one in the left main stem, 2–3 in the circumflex/obtuse marginal system, 3–4 in the LAD/diagonal system, and one if a ramus intermedius was present. Patients were excluded if the baseline angiogram revealed any disease, if the repeat coronary angiogram was within 12 months of baseline or if they were under cardiac transplant follow up. Demographic, clinical and angiographic data were collected from hospital records. Hypertension and hypercholesterolemia were defined by the presence of anti-hypertensive and lipid-lowering drugs, respectively. Outcome data were collected from the Office of National Statistics (for mortality), the hospital database and patient notes.

Data Analysis

Data are presented as mean ± SD, median (IQR) or as percentages (proportions) unless stated otherwise. Analysis was carried out using Students *t* test or one-way ANOVA for continuous variables and Chi squared or Fisher's exact test for categorical variables. Variables with significant trends ($P < 0.1$) were entered into a logistic regression model to identify factors independently associated with disease progression. All statistical analysis was performed using SPSS version 21 (IBM, SPSS, NY, USA). Confidence intervals for proportions were calculated using the exact method (Biometrika 26:404–413, 1934)

RESULTS

Patient Characteristics

Six thousand and sixty-eight patients were identified as having had a coronary angiogram reported by the operator as normal between 2004 and 2013. Of these, 162 underwent repeat procedures after at least 12 months from the first procedure. 99 of these were identified to be truly normal after re-analysis by a single experienced investigator (JG). Two patents were excluded because they had undergone cardiac transplantation and were subject to regular surveillance angiography. For the remaining 97, the median age at first procedure was 60 (IQR 53–67) and 42% were male. Median (and mean) follow up was 51 (IQR 39–68) months. 60% (58/97) of repeat angiograms were performed for the assessment of chest pain, of these 36% (21/58) were performed urgently and 64% (37/58) as elective procedures. Just 28% (16/58) of those presenting with chest pain underwent non-invasive imaging prior to their repeat angiogram. Of those presenting acutely, 48% (10/21) were referred with troponin positive chest pain, 14% (3/21) with chest pain associated with ischemic ECG changes, and 38% (8/21) with suspected unstable angina. Of the remaining 40% of patients, 33% (32/97) underwent repeat angiography as pre-operative assessment, 4% (4/97) for the investigation of arrhythmia, and 3% (3/97) as part of work up

TABLE I. Clinical Characteristics of Patients Undergoing Repeat Angiography Stratified by the Presence of Disease Development

Variables	No disease development at repeat CAG	Evidence of CAD development at repeat CAG	P*
Number of patients	87 (90%)	10 (10%)	
Age (years)	59.0 ± 11.2	61.4 ± 8.0	0.51
Male	36 (41%)	5 (50%)	0.42
Presentation (1st procedure)			0.69
Chest pain	64 (74%)	9 (90%)	ns
Pre surgery	17 (20%)	1 (1%)	ns
Heart Failure	3 (3%)	0 (0%)	ns
Arrhythmia	3 (3%)	0 (0%)	ns
Presentation (2nd procedure)			0.80
Chest pain	52 (60%)	7 (70%)	ns
Pre surgery	28 (32%)	3 (30%)	ns
Heart Failure	3 (3%)	0 (0%)	ns
Arrhythmia	4 (5%)	0 (0%)	ns
Urgency (1st procedure)			
Urgent	24 (28%)	2 (20%)	0.61
Elective	63 (72%)	8 (80%)	ns
Urgency (2nd procedure)			
Urgent	22 (25%)	2 (20%)	0.53
Elective	65 (75%)	8 (80%)	ns
Time between procedures (m)	50.8 ± 22.5	69.0 ± 12.9	0.01
Diabetes Mellitus	75 (86%)	8 (80%)	0.44
Hypertension	57 (66%)	5 (50%)	0.32
Dyslipidaemia	59 (68%)	9 (90%)	0.03
PVD	3 (3%)	2 (20%)	0.08
Previous stroke	7 (8%)	0 (0%)	0.45
Smoker	23 (26%)	6 (60%)	0.04
Positive functional test	15 (17%)	5 (50%)	0.56

CAD, coronary artery disease; CAG, coronary angiography; PVD, peripheral vascular disease

for heart failure diagnosis. The comparison of patient characteristics, stratified by the presence of disease development, is shown in Table I.

Incidence of Disease Development

At follow-up coronary angiography, of the 97 patients, 10 (10.3%) had some disease development (defined as 1–50% diameter stenosis) in a mean 1.2 segments; a risk of 0.10 (95% CI 0.05–0.17). No patients developed significant disease (>50% in 2, or >70% in 1 view); a risk of 0% (95% CI 0.00–0.04). The results of the QCA analysis for the patients that developed disease are shown in Table II. Five patients died since the second coronary angiogram was performed. These were all in the group with no disease development. None of the five had coronary artery disease as an attributed cause of death.

Risk Factors for Disease Development

Risk factors for disease development were identified at univariate analysis as time between procedures, hypercholesterolemia, peripheral vascular disease, and smoking ($P < 0.1$). These were entered into a logistic regression model alongside age and sex. Age, smoking and the time elapsed between angiograms were identified as independent predictors of disease development as shown in Table III. Hypercholesterolemia, diabetes, the indication for coronary angiography, urgency of presentation, and a positive functional imaging test were not predictors of disease development.

DISCUSSION

In this 'real world', observational study of 97 patients with a baseline truly normal coronary angiogram and a subsequent coronary angiogram, we found that only 10% of patients with originally normal coronary angiograms demonstrated any degree of progression over a median of 51 months follow up, but none was significant according to 'eyeball' or QCA assessment. The risk of development of any disease was identified as 0.10 (95% CI 0.05–0.17) with a risk of development of significant disease of 0.00 (95% CI 0.00–0.04). Thus, 51 months after normal coronary angiography there is only a 0–4% risk of developing significant disease even in patients who for one reason or another (chest pain in 60%) re-presented. In those who did not (likely to be a larger number) these risks might be even smaller. Smoking, advanced age, and time between angiograms were independent predictors of disease development. This is the first time that the natural history of normal coronary arteries has been analyzed in the contemporary era.

A few decades-old studies have attempted to elicit the fate of normal coronary arteries. These studies of limited size did not separate patients with mild disease from those with completely normal vessels [7,8]. One study in 1976 suggested that up to 67% of all disease remains stable over an average of 39 months [9]. Another in 1974, found that 44/46 patients with normal coronary angiograms demonstrated no progression over a median of 52 months [10]. With significant advances in prevention measures these studies now demand confirmation. More recently, Pitts et al. [11] evaluated 17 patients with a previously normal coronary angiogram, who underwent repeat coronary angiography for the evaluation of chest pain. During an average time of 8.9 years, just two patients developed coronary artery disease. Thus, 88% (15/17) of patients did not develop any disease. Based on these results, they suggested that repeat angiography in patients with previously normal angiograms is rarely warranted. However, to our knowledge no larger or more recent studies in normal coronary arteries have been carried out, and in

TABLE II. Results of QCA Analysis in Those With Disease Development at Repeat Angiography

Patient number	Age (years)	Sex	Time to repeat CAG (months)	Presentation urgency	Indication for repeat	QCA view 1	QCA view 2	No. of segments
1	66	M	17	Elective	Chest pain	40%	39%	1
2	58	F	58	Elective	Chest pain	32%	30%	1
3	53	M	61	Elective	Chest pain	19%	23%	1
4	51	F	62	Elective	Chest pain	48%	48%	1
5	65	M	62	Elective	Chest pain	40%	40%	1
6	71	F	67	Elective	Pre AVR	34%	51%	1
7	68	F	69	Elective	Pre AVR	23%	34%	2
						31%	46%	
8	69	M	73	Urgent	Chest pain	45%	65%	1
9	67	F	85	Urgent	Chest pain	9%	28%	1
10	50	M	97	Elective	Chest pain	23%	36%	2
						40%	56%	

CAG, coronary angiography; AVR, aortic valve replacement; QCA, quantitative coronary angiography

TABLE III. Independent Predictors of Disease Development

		95.0% CI for OR		
	OR	Lower	Upper	Sig.
Age	1.18	1.04	1.35	0.01
Sex	4.73	.65	34.54	0.13
Smoking	0.02	0.00	0.23	<0.01
Hypertension	6.61	0.99	43.99	0.05
Time to repeat (months)	1.07	1.02	1.12	<0.01

everyday practice we continue to subject these patients to repeat procedures.

Smoking status emerged as the strongest predictor of disease progression. This has been demonstrated in other studies. Levitt et al. [5] analyzed 2,718 patients undergoing cardiac catheterization for stable angina and highlighted absence of smoking, as well as female sex, absence of diabetes, hyperlipidemia, and peripheral vascular disease as independent predictors of normal angiography. In our study, the time between angiogram was also predictive. We found that the odds ratio for disease development was 2.23 per year.

Even in patients that presented with chest pain with a prior normal coronary angiogram, there was only a 12% incidence of the appearance of coronary artery disease on the repeat coronary angiogram (95% CI 0.04–0.22) and 0.00% (95% CI 0.00–0.06) risk of significant disease. Based upon the National Institute for Health and care excellence (NICE) guidelines for the assessment of chest pain, only those with an estimated likelihood of 61–90% should proceed to invasive angiography [12]. In fact, patients with a risk of 12% would not even be deemed high enough risk to undergo non-invasive functional imaging. Current guidelines do not take into consideration previous angiography results. Our results suggest that this is worth considering. Additionally, many patients who undergo repeat angiography following a positive functional imaging test continue to have normal arteries. Although the negative predictive value of non invasive imaging techniques has been consistently high in studies, the positive predictive values have been variable. Indeed, a recent study demonstrated the positive predictive value of CT coronary angiography (CTCA) in patients with low-intermediate risk of CAD of just 40% [13]. Thus, a large proportion of patients are still being referred for angiography where it is probably not warranted. Indeed, in our study a positive functional imaging result was not an independent predictor of disease development.

The second most numerous (32%) indication for repeat angiography was as part of pre-assessment for cardiac surgery. In this group there was 10% incidence of disease on repeat angiography (95% CI 0.02–0.26) and no patients demonstrated significant disease (95% CI 0.00–0.11). There were five patients who underwent initial angiography for work up for valve replacement that did not proceed to operation at that time. When they were re-listed for surgery (between one and 4 years later) they all underwent repeat coronary angiography despite their previous normal result and there being no change in their clinical condition. All their results were normal. Of these patients the mean age was 61 and only one had any significant risk factors. Pre-surgical repeat coronary angiography is probably unnecessary if an original coronary angiogram was normal, at least within the previous 4 years.

STUDY LIMITATIONS

This was a retrospective observational study. In addition, we did not include patients that had not undergone a repeat coronary angiogram, potentially introducing bias. Due to the observational nature of the study the follow up times differed between patients.

Furthermore intracoronary imaging (Intravascular ultrasound, optical coherence tomography) was not used. Also, coronary angiography is limited by its spatial resolution to assessment of large and medium sized coronary arteries, and is unable to delineate microvascular disease. Finally our sample size was small, with no patients developing significant disease. A larger, cross-centre study would complement this study.

CONCLUSION

Normal coronary arteries rarely progress to significant disease within 4 years and the likelihood of some disease developing within that time period is increased with advanced age, time from the original coronary angiogram, and smoking status. There is no indication for repeat angiography in patients with a previously normal coronary angiogram in the absence of significant risk factors regardless of the presence of symptoms within 4 years. Many patients are undergoing repeat procedures unnecessarily.

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