

## A retrospective cohort of coronary artery disease development after at least two angiograms in patients with normal coronary angiograms or mild coronary artery disease

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### Abstract

**Background:** Coronary Artery Disease is one of the leading causes of death in the world. CAD usually progresses slowly during time and patients with normal or near-normal coronary arteries are also at risk of developing CAD. It is now believed that even mild atherosclerosis can increase the rate of CAD.

**Methods:** This is a retrospective, descriptive and analytic study. We selected patients who had undergone at least two diagnostic coronary angiographies at Tehran Heart Center and had normal coronary structure or mild CAD in initial angiography. The data was obtained from the Tehran Heart Center Angiography Databank. Predicting factors in the development of CAD were determined.

**Results:** Data on 556 patients were reviewed. The median interval between the initial and final coronary catheterization was 37.6 months. On the final evaluation, 216 patients (38.8%) found to have developed some degrees of coronary artery disease. Based on the multivariate analysis, age, hematocrit, cigarette smoking, hypertension, and initial presentation with stable and unstable angina were found to be independent predictors of progression to CAD in patients.

**Conclusion:** In the end, 40% of patients who had normal coronary arteries or minimal CAD in the initial angiography report, developed some degrees of CAD and some clinical indices can predict the risk of CAD.

**Keywords:** Coronary artery disease; Angiography; Disease progression predictors; Normal coronary arteries

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Cardiovascular diseases including myocardial infarction (MI) and stroke are the most common causes of death in the world (1). Atherosclerosis, the pathologic process that causes cardiovascular events, is believed to be an inflammatory process and its development is related to multiple factors such as diabetes mellitus, cigarette smoking, hypertension, dyslipidemia and lack of physical activity (2). It is now believed that the process of atherogenesis begins in childhood with the development of fatty streaks and the lesions of atherosclerosis advance with aging. Also, some factors such as the ones mentioned above can accelerate this process and lead to the stenosis of cardiac or cerebral vessels (3-5). Pathological studies of uncut coronary arteries from the hearts of 94 American male combat casualties (mean age, 20.5 years) in Korean War was the first evidence that showed the role of atherosclerosis in CAD (6).

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Similar results were found in the Bogalusa Heart Study (7) and the study of Pathobiological Determinants of Atherosclerosis in Youth (PDAY Study) (8). The latter study covered 1277 subjects aged 5-34 years, of both sexes, from both developed and developing countries who had died of noncardiac causes (such as trauma or suicide). The results showed that the development of fatty streak is higher for the age group 15-25 years, while raised lesions begin developing slowly during the second decade of life, progress steadily during the third, and then more rapidly during the fourth (8) *Watanabe et al.* performed 3-dimensional intravascular ultrasound (3D-IVUS) analysis in 42 heart transplantation recipients and donor-transmitted atherosclerosis (DA) was observed in 57.1% of 42 recipients. The DA group exhibited a significantly greater increase in plaque volume at 1-year post-heart transplantation (9). In some patients, coronary artery disease, if present, progresses slowly with time. Studies have showed that the absence of cardiovascular risk factors of CAD in middle-aged patients is associated with a good cardiovascular prognosis (5). Participants in the Framingham Heart Study who did not have subclinical coronary artery disease and major risk factors were in less risk for CAD by the age of 50 and had longer median survival rates compared to those who had two or more major risk factors (10).

The importance of understanding the clinical course of patients with normal or near-normal coronary arteries in coronary angiogram, was shown in a study done by *Patel et al.* (11). In this study, 398978 patients from 663 hospitals in the American College of Cardiology National Cardiovascular Data Registry, without known coronary artery disease who were undergoing elective catheterization were selected. The study showed that 39.2% of patients had no coronary artery disease (defined as <20% stenosis in all vessels).

Rao Golla et al. concluded that even mild atherosclerosis on the initial angiogram increased the rate of development of CAD by 10-fold, the rate of MI approximately by 3-fold and the rate of revascularization by 8-fold.(12) However, Rowe et al.(13), Jespersen et al.(14) and Moreyra et al.(15) showed that patients with normal or near-normal coronary arteries have a low rate of myocardial ischemic events and have significantly longer survival than matched subjects from the general population. In a study done by McMullan et al. it was revealed that of all traditional risk factors for CAD, only diabetes was associated with a higher risk of death (16). Six (40%) out of 15 patients who were undergoing repeat angiogram within five years developed new CAD, with one

requiring revascularization. In another study, risk factor analysis concluded that cigarette smoking correlated significantly with the formation of new lesions ( $P=0.001$ ), whereas total cholesterol is correlated with further progression of preexisting stenosis ( $P=0.017$ ) but not with the incidence of new lesions (17).

The incidence rate of atherosclerosis has not yet been determined in patients with unremarkable angiograms, especially the elderly. Identifying patients with low long-life risk factors for CAD could be of great importance in public health policy-making to prevent coronary artery diseases and improve the quality of life in patients suffering from them. Thus, this cohort study was designed to assess the course of atherosclerosis in patients with normal epicardial coronary arteries (NECA) or mild CAD who had undergone at least two coronary catheterizations at Tehran Heart Center that had significant atherosclerotic risk factors and to determine the risk factors of CAD development.

## Methods

**Trial Design and Study Population:** This retrospective cohort study was conducted at Tehran Heart Center and our sampling method was convenience sampling. Patients with complete data on diagnostic cardiac catheterization for the period between January 2005 and December 2016 were available, had undergone at least two diagnostic coronary angiographies at Tehran Heart Center and been diagnosed with normal coronary artery structure or mild CAD in the first angiogram were included in the study. Information was collected on the patients' age, gender, body mass index (BMI), cardiovascular risk factors including diabetes mellitus, hypertension, dyslipidemia, cigarette smoking, opium use, family history of CAD, also laboratory indices including fasting blood glucose (FBS), lipid profile (including total cholesterol, high density cholesterol, low density cholesterol, triglyceride), plasma creatinine levels and complete blood count (CBC) from Tehran Heart Center Databank. All measurements were done in THC's central laboratory. In cases where there were multiple set data available, the most recent set (i.e. data at the time of second angiography) has been used.

Each patient's catheterization procedure was done via right femoral artery access, standard angiography projections were obtained (with more projections getting obtained whenever the patient's anatomy required it), nitroglycerine

injection was not a routine part of our procedures. Patients' first and second angiographic reports were obtained from Tehran Heart Center Angiography Databank and indices such as the involved artery, severity and number of arteries involved and other indices like ejection fraction, angiography date, patients' initial clinical manifestations and co-existing disorders were included. To have more precise data, we determined the severity of each segment of each artery by subjective assessment of coronary stenosis using manual verification by two skilled cardiologists (one of them being an interventionist). Whenever there was a significant discrepancy between these two cardiologists' assessment, we rechecked the results with the initial databank report and then asked a third cardiologist to assess the angiogram one more time. The final result that was used for the purpose of this study was the "best of three", although it must be noted that these situations were rare.

**Explanatory Variables:** Patients' demographic characteristics including age and gender, height and body weight, past medical history of cardiac and non-cardiac diseases and laboratory indices were defined as the variables of this study. In addition, the second angiographic report, the existence of CAD and the severity of CAD in each segment of each coronary artery were recorded. The course of coronary artery disease in patients is the main variable of the study. Intermediate variables were divided into two categories: uncontrollable variants including age, gender, family history; and controllable variants including diabetes mellitus (DM), hypertension, cholesterol and triglyceride levels, BMI and stress levels.

**Sample size:** All patients who had undergone at least two diagnostic cardiac catheterizations at Tehran Heart Center between January 2005 and December 2016 and been diagnosed with normal coronary artery structure or mild CAD were included in the study. Assuming a two-sided significance level of 0.05 and a standard power of 95%, a sample size of 500 was calculated.

**Statistical Analysis:** A categorical variable was presented as a number of patients and as a percentage. Continuous variable was reported as mean  $\pm$  standard deviation (SD) unless stated otherwise and mean (95% confidence intervals, 95%CI) was used to report mean difference. The data were managed and analyzed using SPSS Statistics Version 18.0 (SPSS Inc. Chicago, IL). To compare continuous variables, the t-test or non-parametric tests were performed. Categorical variables were compared using Fisher's exact test or the chi-square test. A  $p < 0.05$  was considered significant.

**Ethical Consideration:** Since data was extracted from patients' files, the confidentiality of their medical and personal information was preserved.

## Results

**Patient characteristics:** Data on 556 patients with normal coronary arteries or minimal CAD reported in their initial angiogram who underwent another diagnostic coronary angiography at least one more time at Tehran Heart Center were gathered. The median interval between the initial and final coronary catheterization was 37.6 months (min: 6.5 months and max: 98.9 months). Typical chest pain was the most common indication for coronary catheterization. Other indications for coronary catheterization are listed in table 1.

**Table 1. Symptoms and indications for coronary angiography in patients**

Indication for CAG or symptom	Frequency (%)
Typical Chest Pain	322 (58)
Atypical Chest pain	132 (23.7)
Candidate for valvular surgery	21 (3.8)
Positive ETT	10 (1.7)
Positive MPI	76 (13.6)
MDCT	11 (1.9)
Syncope	10 (1.8)
Unstable Angina	4 (0.7)
STEMI	2 (0.4)
Fatigue	45 (8.1)
Dyspnea on effort	314 (56.5)
Non-angina chest pain	3 (0.5)
Heart failure	21 (3.7)

**Incidence of Disease Development and Risk Factors:** At the time of the last coronary angiography, 216 (38.8%) out of 556 patients were found to have developed some degrees of coronary artery disease. Results of the final coronary angiography of patients are shown in figure 1.

Patients were divided into two groups based on the final angiographic reports: a. normal vessel or mild coronary artery disease group and b. CAD group. The parameters mentioned in the previous section were compared between two groups and risk factors for disease development were identified using univariate regression analysis. That result is shown in table 2. Multivariate analysis was done using the variables with  $p < 0.1$  to identify independent predictors of CAD development.

Based on the multivariate analysis, patient's age, hematocrit, cigarette smoking, hypertension, and initial presentation with

stable and unstable angina were found to be independent predictors of progression to CAD.

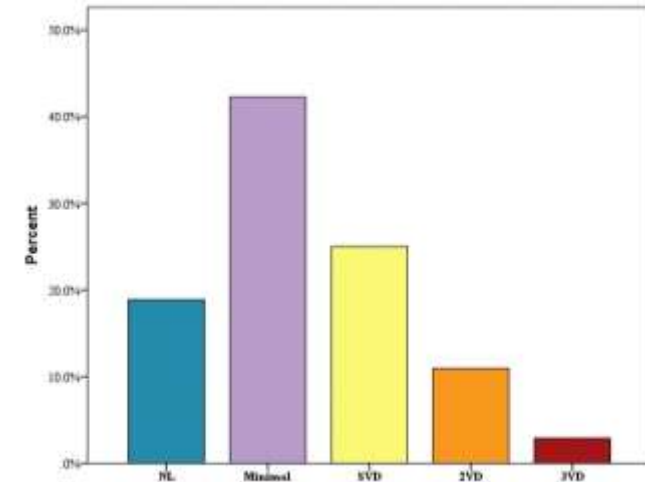


Figure 1. Results of the final coronary angiography of patients

Table 2. Results of univariate analysis of risk factors for developing CAD

Characteristic	Normal vessel (n=340)	CAD (n=216)	HR	95.0% confidence interval		P-value
				Lower	Upper	
Age	57.6 (9.3)	28.6 (4.6)	1.013	0.998	1.028	0.089
Male gender	180 (52.9)	132 (61.1)	1.259	0.957	1.656	0.1
BMI	28.6 (4.6)	29.1 (5.0)	1.029	0.998	1.06	0.063
Creatinine	0.96 (0.47)	0.98 (0.45)	0.995	0.732	1.353	0.975
Hemoglobin	13.9 (1.7)	14.4 (2.6)	1.065	1.017	1.115	0.007
Hematocrit	41.2 (4.9)	42.1 (5.0)	1.035	1.008	1.064	0.011
Fasting blood sugar	103 [92, 126]	10.6 [93, 132]	1	0.998	1.002	0.977
HDL	43.0 (13.9)	40.9 (10.3)	0.99	0.978	1.002	0.102
LDL	105.1 (36.9)	112.5 (77.2)	1.002	1	1.004	0.107
Total cholesterol	173.7 (44.9)	176.5 (77.3)	1	0.996	1.003	0.768
Triglyceride	134.0 [98.5, 193.5]	142 [107, 196]	1	1	1.001	0.241
Non-smoker	254 (74.7)	143 (66.2)				0.024
Previous smoker	40 (11.8)	29 (13.4)	1.424	0.953	2.129	0.085
Current smoker	46 (13.5)	44 (20.4)	1.521	1.084	2.136	0.015
Diabetes mellitus	94 (27.6)	69 (31.9)	1.248	0.936	1.664	0.13
Family history of CAD	58 (17.1)	38 (17.6)	1.028	0.724	1.461	0.877
Hyperlipidemia	221 (65.0)	147 (68.1)	1.144	0.859	1.524	0.358
Hypertension	185 (54.4)	135 (62.5)	1.417	1.074	1.87	0.014
Opium	311 (91.5)	197 (91.2)				0.335
Former opium user	7 (2.1)	5 (2.3)	1.496	0.615	3.641	0.375
Current opium user	22 (6.5)	14 (6.5)	1.404	0.815	2.421	0.221
Aspirin	273 (80.3)	184 (86.0)	1.419	0.964	2.089	0.076
Acute chest pain	81 (23.9)	55 (25.5)	1.351	0.993	1.838	0.056
Dyspnea on effort	196 (57.6)	112 (51.9)	0.918	0.701	1.2	0.531
TCP	189 (55.6)	112 (51.9)	0.872	0.666	1.141	0.317
NSTEMI	6 (1.8)	6 (2.8)	1.054	0.468	2.378	0.898
Stable angina	104 (30.6)	52 (24.1)	0.691	0.504	0.948	0.022
STEMI	7 (2.1)	6 (2.8)	1.004	0.445	2.268	0.991
Unstable angina	38 (11.2)	29 (13.4)	0.671	0.45	0.999	0.049

**Table 3. Independent Predictors of CAD Development**

Characteristic	Hazard ratio	95.0% confidence interval		P-value
		Lower	Upper	
Age	1.018	1.002	1.035	0.025
BMI	1.031	1	1.063	0.053
Hematocrit	1.037	1.009	1.066	0.009
Nonsmoker				0.004
Past smoker	1.659	1.1	2.503	0.016
Current smoker	1.699	1.166	2.476	0.006
Hypertension	1.392	1.044	1.858	0.024
Acute chest pain	1.363	0.992	1.872	0.056
Stable angina	0.631	0.454	0.879	0.006
Unstable angina	0.54	0.355	0.821	0.004

## Discussion

This study shows that patients who had normal coronary arteries or minimal CAD according to their initial coronary angiogram were still at risk of developing CAD through time. Risk factors such as old age, high hematocrit, cigarette smoking, hypertension and initial presentation with stable and unstable angina play a major role in the progression of atherosclerosis into CAD.

Several studies have shown that eliminating the risk factors of cardiovascular diseases (CVD) which are known to cause endothelial dysfunction had a key role in both primary and secondary prevention of CVD (18, 19), meaning that improvement of endothelial function leads to decrease in cardiovascular events. Mechanisms by which endothelial dysfunction can cause cardiovascular events are multiple. One possible explanation is myocardial ischemia might still occur due to endothelial dysfunction while there might be no evidence of obstructive coronary artery disease (20, 21). In fact, it has been shown that decreased response of coronary blood flow to acetylcholine due to coronary endothelial dysfunction is associated with defects in coronary blood flow. This study demonstrated the potential importance of risk factors that can cause endothelial dysfunction which in turn plays a major role in the development of atherosclerosis. We can assume that endothelial dysfunction represents the accelerated level of atherosclerosis and this is due to the physiological and protective roles of endothelial cells. Abnormal responses of the endothelium to vasodilatory effects of acetylcholine can be caused by decreased bioavailability of nitric oxide (22-24). Therefore, we can say despite the fact that atherosclerosis is partly reversible, in patients who have normal coronary artery or minimal CAD in

their angiography report, it is a progressive process and if left untreated can lead to coronary artery disease.

On the other hand, coronary catheterization provides a diagnostic and therapeutic opportunity for cardiologists. Many physicians try to assess the risk of coronary artery incidents in patients who show signs and symptoms of coronary syndrome, using the reports of coronary angiography. Although coronary catheterization is claimed to be the gold standard diagnostic procedure, it is not 100 percent accurate. A great number of vessels which are angiographically normal have been shown to be atherosclerotic by intravascular ultrasound (25, 26). Compensative enlargement of LAD may cause normal angiographic views (even in the presence of coronary artery disease); because lumen stenosis may be delayed until the lesion occupies 40 percent of the internal elastic lamina area (27). When coronary artery disease is confirmed, more intensive treatment is needed to prevent cardiovascular events even if interventional treatment is not indicated.(28) Thus, additional non-cardiac evaluations and if indicated treatment of patients who have had angiographically normal coronary arteries is recommended. Normally, patients who have had normal coronary arteries in angiography are considered low risk for cardiovascular morbidity and mortality, nevertheless, recent studies support the opposite (29-35). These studies had relatively small sample sizes and mostly focused on young patients who did not have co-existing diseases, so the possibility of disease development in short-term follow-up seems to be low. In our study, the follow-up period was relatively long and patients with classic cardiovascular risk factors were not eliminated. Thus, it can show independent predictive factors of CAD development in a patient with

normal coronary arteries or minimal CAD in initial angiography in a better way.

Our study has some limitations which single center unicentric study and study population only included patients who returned to Tehran Heart Center for further coronary angiographies, therefore it was not possible to follow-up all patients. Also, our study was based on angiography reports in Tehran Heart Center databank and it is possible that human error in coronary angiography reports misrepresent the results. And finally, it must be noted that assessing coronary catheterization results via objective methods will definitely yield a more accurate interpretation of coronary artery disease severity and using this method can be a goal in future studies.

According to the results, we can conclude that 40% of patients who had normal coronary arteries or minimal CAD in the angiography report, ultimately developed some degrees of CAD. Risk factors including old age, high hematocrit, cigarette smoking, hypertension, and initial presentation with stable and unstable angina can independently predict the probability of progressing into coronary artery disease.

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