



Original Article

Incidence, predictors, clinical profile, management and outcome of patients with isolated left main coronary artery ostial disease

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ABSTRACT

Objectives: Isolated left main coronary artery (LMCA) ostial disease is a rare variant of LMCA disease. Earlier studies on this disease are limited by small number of patients enrolled. The aim of the present study was to analyze the incidence, risk factors, clinical profile and long term outcome of patients with isolated LMCA ostial disease.

Methods: 15,553 patients who underwent coronary angiogram in a single tertiary care cardiac hospital were analyzed for LMCA disease. 351(2.2%) patients were found to have significant LMCA disease out of which 28(0.18%) had isolated LMCA ostial disease. These 28 patients were compared with 323 non-ostial and non-isolated LMCA disease patients.

Results: The mean age of isolated LMCA ostial disease group was significantly less than the other group ($p=0.009$). Females were more affected than males ($p=0.008$). They also had low incidence of coronary risk factors (especially dyslipidemia, $p=0.04$). They tend to present more with stable angina and less with myocardial infarction. They had higher ejection fraction and normal regional wall motion ($p=0.04$). There was no mortality difference between two groups at the end of 1 year ($p=0.234$).

Conclusion: In one of the largest studies done in these patients, we found that isolated LMCA ostial disease is more common in middle aged females with few coronary risk factors. These patients also had a better ejection fraction and normal regional wall motion compared to patients with non-ostial and non-isolated LMCA disease. The clinical and angiographic profile of these patients suggests that they may represent a distinct clinical entity.

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Introduction

Left main coronary artery (LMCA) disease remains an important risk factor for increased mortality and morbidity at all stages of diagnosis and treatment of coronary artery disease. Significant LMCA stenosis was found in 2.5–17.5% of patients undergoing cardiac catheterization in various clinical presentations.^{1–5} LMCA narrowing mostly occurs beyond the ostium in the mid-portion or at the bifurcation, where it can extend to both major branches.^{6,7}

The incidence of isolated coronary ostial stenosis has varied between 0.13% and 2.7%.^{8,9} In the majority of cases there is coexisting disease in multiple coronary vessels. Isolated LMCA ostial stenosis is a rare condition.^{7,10} Its incidence has been reported to be between 0.05%–0.88% in various studies.^{6,8,11,12} It is more commonly reported in women, usually before menopause. Atherosclerosis has been considered as its most likely cause.^{8,13,14} Other rare causes of ostial stenosis include fibromuscular dysplasia,¹² syphilitic aortitis,^{15,16} Takayasu arteritis,^{17–19} aortic valve disease²⁰ and iatrogenic causes, such as mediastinal irradiation,²¹ cardiac surgery^{22–24} or percutaneous interventions.²⁵ In general the natural history of the isolated LMCA ostial disease is poor.²⁶ Early recognition and appropriate treatment will alter the unfavourable natural course of the disease. Majority of the earlier studies done on isolated LMCA ostial disease are limited by small number of patients enrolled.^{6–8,10} The aim of the present study was to analyze the incidence, risk factors, demographics,

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clinical profile and long term outcome of patients with isolated LMCA ostial disease.

2. Methods

2.1. Patient selection

In this retrospective study the database of cardiac catheterization laboratory in a single tertiary care cardiac hospital was reviewed to identify patients with LMCA disease. Out of 15,553 patients who underwent conventional coronary angiogram for various reasons between January 2011 to June 2012, 351 (2.2%) were found to have significant LMCA disease. Among these 351 patients, 28 (0.18%) were found to have isolated LMCA ostial disease. The diagnosis of isolated LMCA ostial disease was based on following 2 criteria. 1) Lesion of $\geq 50\%$ diameter stenosis of left main coronary ostium. 2) The remaining major coronary arteries and their branches exhibited in multiple projections, a patent lumen without any evidence of atherosclerotic plaques.

Patients were divided into 2 groups- patients with isolated LMCA ostial disease and patients with Non-ostial LMCA disease. A detailed review of all patients according to their medical records was performed. All patients were analyzed for demographic data, risk factors, clinical profile, treatment and 1 year mortality. Hypertension was defined as systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg and/or on antihypertensive treatment. Diabetes mellitus was described as fasting plasma glucose ≥ 126 mg/dl and/or on antidiabetic drugs. Dyslipidemia was defined as total cholesterol > 200 mg/dl and/or LDL cholesterol > 160 mg/dl without risk factors and > 100 mg/dl with risk factors, HDL < 40 mg/dl or on anti hyperlipidemic drugs.²⁷ Family history (first-degree relatives age < 55 years in men and < 65 years in women), smoking (current smoker or quit less than 30 days before), and obesity (body mass index > 30 kg/cm²)²⁸ were also noted. Acute myocardial infarction (MI) was defined as chest pain lasting ≥ 20 min and satisfying the World Health Organization criteria of acute MI. Trans-thoracic echocardiogram was used to measure LV ejection fraction and assess regional wall motion abnormalities.

2.2. Coronary angiogram

Selective coronary angiography was performed using Judkin's catheters via the femoral route in all patients. Left anterior oblique, right anterior oblique and anterior caudal views were recorded in every patient. Ostial lesion was defined as a proximally significant stenosis up to 3 mm from the coronary origin.⁹ Non-ostial lesion was defined as significant stenosis distal to 3 mm from the coronary origin.⁹ Any subtle change in pressure waveform as the catheter engaged the ostium of LMCA was carefully noted. To exclude the possibility of catheter induced spasm, intracoronary nitroglycerin 200 mcg was routinely administered to all patients when stenosis was visualized and performed a coronary angiogram 2 min later and measured the extent of the stenosis. Patients were classified as having 1, 2 or 3 vessel disease, based on the presence of $\geq 50\%$ diameter stenosis in the major three coronary arteries.¹⁰ The coronary angiograms were reviewed by four experienced operators who reached agreement on the identification of any obstructive lesion within coronary vessels.

Patients with coronary ostial stenosis secondary to syphilitic aortitis, takayasu aortitis, aortic valve disease and iatrogenic causes were excluded from the study after taking detailed history and doing appropriate investigations. Ethical committee clearance was taken before conducting the study. Informed consent was taken from all patients. Mean follow up was 1 year and 100% complete. It

was at regular intervals with clinical visits or telephone interviews. No angiographic follow up was done.

3. Statistics

Categorical variables were compared using the chi square test and the Fisher exact test, as appropriate. Continuous variables were analyzed using two-tailed *t*-test or Mann-Whitney *U* test. Patient characteristic variables were expressed as means \pm standard deviation and percentages. Only factors significant in univariate testing were included in the multivariate model. Multivariate logistic regression analysis was used to determine significant factors associated with isolated LMCA ostial disease. A two tailed *p*-value less than 0.05 was used to indicate statistical significance. Statistical analysis was performed using SPSS statistical software (version 16.0, SPSS Inc., Chicago, Illinois).

4. Results

4.1. Demographics

Out of total 15,553 patients who underwent coronary angiogram 351 (2.2%) were diagnosed to have significant LMCA disease. Among these 351 patients 28 (0.18%) were found to have isolated LMCA ostial disease. The baseline clinical demographics of these patients are given in Table 1. The mean age of patients with isolated LMCA ostial disease was significantly less than the patients with non-ostial LMCA disease. (50.46 ± 13.2 years vs. 59.45 ± 10.0 years, $p \leq 0.0001$). Out of 28 patients with isolated LMCA ostial disease 15 (53.57%) were females compared to 62 (19.19%) of 323 with non-ostial disease ($p \leq 0.0001$) indicating significant proportion of patients with isolated LMCA ostial disease were females.

4.2. Risk factors

Univariate analysis showed that coronary risk factors like hypertension, dyslipidemia, diabetes and past history of coronary artery disease (CAD) were significantly less in patients with isolated LMCA ostial disease compared to patients with non-ostial LMCA disease. In multivariate analysis dyslipidemia was found to be significantly associated with the latter group ($p = 0.04$). There was no significant difference between the groups with respect to other risk factors like smoking, obesity, peripheral vascular disease and family history of CAD.

4.3. Clinical profile

There was no significant difference between the groups with respect to presentation like stable angina ($p = 0.263$), unstable angina ($p = 0.478$), Non ST elevation myocardial infarction ($p = 0.577$) or ST elevation myocardial infarction ($p = 0.327$), though patients with isolated LMCA ostial disease tend to present more with stable angina and less with myocardial infarction.

Patients with isolated LMCA ostial disease had a significantly more ejection fraction (55.86% vs. 51.71% , $p = 0.010$) and normal regional wall motion ($p = 0.002$) in univariate analysis. In multivariate analysis, isolated LMCA ostial disease had significantly higher normal regional wall motion ($p = 0.04$). They also had a lower creatinine levels ($p = 0.004$) when compared to non-ostial LMCA disease group in univariate analysis.

4.4. Coronary angiography

Dampening of the pressure recordings during cannulation of the left coronary ostium was reported in all 28 patients. All patients underwent cardiac catheterization without any major

Table 1
Baseline clinical demographics.

Variable	Isolated LMCA ostial disease (n=28)	Non-ostial and non-isolated LMCA disease (n=323)	Univariate analysis p-value
Age (mean ± SD) (range)	50.46 ± 13.2 (31–78)	59.45 ± 10.0 (34–85)	<0.0001
Sex			<0.0001
Female	15 (53.57%)	62 (19.19%)	
Male	13 (46.42%)	261 (80.80%)	
Clinical presentation			
Stable angina	16 (57.14%)	149 (46.13%)	0.263
Unstable angina	4 (14.28%)	64 (19.81%)	0.478
NSTEMI	4 (14.28%)	35 (10.83%)	0.577
STEMI	5 (17.85%)	78 (24.14%)	0.327
Risk factors			
Hypertension	9 (32.14%)	184 (56.96%)	0.011
Diabetes mellitus	9 (32.14%)	169 (52.32%)	0.040
Dyslipidemia	10 (35.71%)	195 (60.37%)	0.011
Obesity	5 (17.85%)	40 (12.38%)	0.406
Smoking	8 (28.57%)	135 (41.79%)	0.172
History of IHD	1 (3.5%)	87 (26.93%)	0.006
History of PVD	0 (0%)	14 (4.3%)	0.261
Family history of IHD	7 (25%)	46 (16.6%)	0.127
Echocardiogram			
Ejection fraction (mean ± SD) (range)	55.86 ± 7.9 (35–61)	51.71 ± 9.1 (25–64)	0.010
RWMA	6 (21.42%)	166 (51.39%)	0.002
Investigations(mean ± SD) (range)			
Urea	26.04 ± 7.8 (17–46)	29.6 ± 13.1 (12–131)	0.189
Creatinine	0.88 ± 0.17 (0.6–1.3)	1.01 ± 0.22 (0.6–2.2)	0.004
Total cholesterol (TC)	174.07 ± 51.8 (120–280)	196.30 ± 56.13 (108–377)	0.050
LDL	110.36 ± 47.05(58–200)	124.74 ± 49.9 (35–300)	0.173
HDL	33.02 ± 6.9 (21–46)	35.10 ± 7.0 (20–65)	0.205
TC/HDL ratio	5.64 ± 2.4 (2.85–10.33)	5.87 ± 2.2 (2.2–12.8)	0.514
Treatment			
CABG	5 (17.85%)	267 (82.66%)	<0.001
PCI	21 (75%)	25 (8.3%)	<0.001
Medical	2 (7.1%)	35 (10.83%)	0.542
Mortality			
30 days	1 (3.57%)	42 (13.0%)	0.144
1 year	2 (7.14%)	50 (15.47%)	0.234

NSTEMI: Non ST elevation myocardial infarction; STEMI: ST elevation myocardial infarction; IHD: Ischemic heart disease; PVD: Peripheral vascular disease; RWMA: Regional wall motion abnormalities; LDL: Low density lipoprotein; HDL: High density lipoprotein; CABG: Coronary artery bypass grafting; PCI: Percutaneous coronary intervention.

complications (dissection, myocardial infarction, cerebrovascular accident or death). In all 28 patients obstruction was confined to the ostium of left main coronary artery. 10 (35.7%) had >90% stenosis, 15 (53.6%) had 70–90% stenosis and only 3 (10.7%) had 50–70% stenosis. In patients with non-ostial LMCA disease 44 (13.62%) had >90%, 163 (50.46%) had 70–90% and 116 (35.91%) had 50–70% stenosis. The ostial lesions were characterized as concentric, short-segment stenosis, in contrast to most of the non-ostial lesions which were eccentric and long segment. There was no angiographically definable collateral circulation from either ipsilateral or contralateral vessels in all patients with isolated LMCA ostial disease.

4.5. Management

Twenty one (75%) patients with isolated LMCA ostial disease underwent percutaneous coronary intervention (PCI) with stenting. Drug eluting stents were implanted in all patients. There were no peri-procedural complications. 5 (17.85%) of them underwent coronary artery bypass grafting (CABG). 2 (7.1%) were managed medically as they were not willing for any procedure. In non-ostial

LMCA disease group 267 (82.66%) underwent CABG, 25 (8.3%) had PCI with stenting and 35 (10.83%) were managed medically.

4.6. Mortality

There was no significant difference in 30 days or 1 year mortality between the two groups. 1 patient in isolated LMCA ostial disease group and 42 patients with non-ostial LMCA disease group were dead at the end of 30 days (3.57% vs 13.0% respectively, $p=0.144$). With respect to 1 year mortality, 2 from isolated LMCA ostial disease group and 50 from non ostial LMCA disease group were dead by the end of 1 year (7.14% vs 15.47% respectively, $p=0.234$). Out of 2 patients who died in isolated LMCA ostial disease group, one died 3 days after CABG, and the other patient who was managed medically died after 4 months. Remaining 26 patients were symptom free and none had stroke or myocardial infarction or revascularization at the end of 1 year.

Factors significantly associated with isolated LMCA ostial disease in univariate analysis were taken for multivariate analysis using binary logistic regression equation. The result of multivariate analysis is illustrated in Table 2. Female sex, younger age, no dyslipidemia and normal regional wall motion were found to be

Table 2
Logistic regression analysis for predictors of isolated LMCA ostial stenosis.

Variable	Univariate analysis p-value	Multivariate analysis p-value	Odds ratio	95% CI
Younger Age	<0.0001	0.009	1.05	1.01–1.10
Female sex	<0.0001	0.008	0.30	0.12–0.72
Dyslipidemia	0.011	0.040	2.52	1.04–6.10
RWMA	0.002	0.040	2.85	1.05–7.77
History of IHD	0.006	0.087	6.07	0.76–48.03
Hypertension	0.011	0.110	2.15	0.84–5.52
Diabetes mellitus	0.040	0.464	1.41	0.55–3.57

RWMA: Regional wall motion abnormalities; IHD: Ischemic heart disease; CI: Confidence interval.

significantly associated with isolated LMCA ostial disease after multivariate analysis.

5. Discussion

Isolated coronary ostial disease is a rare disease. The incidence has varied between 0.13% and 2.7%.⁸ Thompson et al.¹⁰ reported 5 patients (0.2%) and Yildirimturk et al.⁹ reported 15 patients (0.5%) with isolated coronary ostial stenosis among 2105 and 2898 cases respectively with angiographically defined coronary disease. This included both right and left coronary ostial stenosis. Topaz et al.²⁹ documented 12 patients (0.06%) and Koh et al.⁸ reported 6 patients (0.88%) of isolated LMCA ostial disease among 21,545 and 684 patients respectively who underwent coronary angiogram. Sasaguri et al.⁶ reported 0.7% of isolated LMCA ostial stenosis among 700 patients who underwent CABG. These studies included small number (<10 in each study) of patients limiting their statistical significance. Mahajan et al.¹¹ reported 30 (0.06%) cases of isolated LMCA ostial stenosis among 44,320 patients who underwent cardiac catheterization. Ours is one of the largest studies done in this group of patients. We found an incidence of 0.18% among 15,553 patients who underwent coronary angiogram.

Most of the studies showed that the main cause of isolated LMCA ostial disease is atherosclerosis especially early atheroma.^{11,30} Koh et al.⁸ showed that in their study of 6 patients, 4 had atherosclerosis on histopathology, a finding consistent with previous reports. Other rare causes include fibromuscular dysplasia,¹² Takayasu's aortitis,^{17–19} syphilitic aortitis,^{15,16} iatrogenic causes,^{21–25} congenital ostial membrane of the left coronary artery³¹ and hypoplasia or atresia of the coronary ostium.^{32–33}

Thompson et al.¹⁰ reported that patients with isolated coronary ostial stenosis are mostly young to middle-aged women who present with severe symptoms of short duration and a low incidence of coronary risk factors. Similar findings were reported by Sasaguri et al.,⁶ Yamanaka et al.¹² and Koh et al.⁸ Mahajan et al.¹¹ reported isolated LMCA ostial disease was common in women and smokers. However Yildirimturk et al.⁹ reported that there was no difference in patients with ostial LMCA and non ostial LMCA stenosis in terms of age, gender and cardiovascular risk factors. Also there was a significant correlation between ostial stenosis of LMCA and right coronary artery. Our study demonstrates that isolated LMCA ostial disease is significantly more common in females. These patients were also younger and had less prevalence of coronary risk factors (especially dyslipidemia) when compared to patients with non-ostial LMCA group. There was no significant difference in clinical presentation between the two groups even though earlier studies showed patients with isolated LMCA ostial stenosis presented with severe symptoms of angina of short duration.

Atherosclerotic coronary artery disease is more common in males than in females. The male/female ratio has been reported to range from 5:1 to 20:1.^{34–36} The reason for increased incidence of isolated LMCA ostial disease in middle age females is not known.

The maximum length of LMCA is usually 4–6 cm.³⁷ Women have smaller LMCA compared to men regardless of body surface area.³⁸ In men the diameter of a non diseased Left main artery is 4.5+/- 0.5 cm, while in women it is slightly smaller at 3.9+/- 0.4 cm.³⁸ The ostium of the LMCA are within the aortic wall and are subject to conditions that affect the aorta.³⁷ Histologically the LMCA ostium lacks adventitia and has considerable smooth muscle and elastic tissue with aortic smooth muscle arranged perpendicular to and surrounding the ostium.¹¹ The higher mean arterial pressure in the aorta may predispose to higher incidence of trauma and intimal injury that leads to atherosclerotic plaque formation.³⁹ In the earliest stage of atheroma development the caliber of the arterial lumen usually does not change appreciably as a result of compensatory enlargement of the outer body of the vessel. Since the ostium is lined by smooth muscle of the aorta rather than the left main artery, atherosclerotic lesions affecting this site may fail to cause compensatory dilatation of the arterial wall resulting in ostial narrowing.¹¹ Another hypothesis believes that an abrupt decrease in estrogen secretion as a result of menopause may play a role in the pathogenesis of premature atherosclerosis.¹² In Yamanaka et al. study,¹² all 8 patients who had isolated LMCA ostial stenosis with normal distal coronaries were having surgical menopause. Our study also showed that 70% of patients had attained menopause when they underwent coronary angiogram. However more research is required to identify the exact cause for female preponderance in this disease.

Cautious approach should be taken when performing coronary angiogram in patients with isolated coronary arterial stenosis. Death, during or immediately after the procedure has been reported in these patients. Cardiologist should be alert to the possibility of coronary ostial stenosis since the catheter tip is frequently positioned beyond the ostial narrowing resulting in misdiagnosis. Therefore angiogram should begin with non-selective injection into the aortic sinus in the shallow left or right anterior oblique projection. Salem et al.⁴⁰ reported that the left coronary ostium is best visualized in the shallow left anterior oblique projection (15–25°) with approximately 20° of craniocaudal tilt. Series of events should alert to the possibility of an ostial stenosis. These includes: 1) difficulty in cannulating the coronary ostium; 2) a profound decrease in distal coronary pressure after coronary engagement with or without angina or the appearance of ST segment changes in the monitoring electrocardiogram; and 3) failure to observe return of contrast medium into the sinus of valsalva after intracoronary injection.¹⁰ Once a left ostial lesion has been demonstrated, only a limited number of other views are advisable, including a right anterior oblique projection.

Despite the crucial anatomic location and severity of the obstructive lesions, we found that the majority of these patients had well preserved cardiac output and normal regional wall motion. This is similar to the reports from Koh et al.,⁸ Thompson et al.,¹⁰ Mahajan et al.¹¹ and Topaz et al.²⁹ Also patients with isolated LMCA ostial disease rarely have collateral circulation from either ipsilateral or contralateral vessels.¹⁰ The unusual

distribution of stenotic lesions in these patients, together with the absence of a defined collateral circulation and short duration of symptoms, suggests the possibility of a rapid development of atherosclerotic lesion.

By virtue of the extensive areas of myocardium placed in jeopardy, patients with coronary ostial stenosis, particularly of the left coronary artery, are at high risk of myocardial infarction and premature death. Medical management has little role to play.⁴¹ Revascularisation, either by surgery or by PCI is the treatment of choice. CABG is the treatment of choice for this condition, with reported 5-year survival rate of >85%.⁴² However, conventional bypass grafting yields some unfavorable sequelae: occlusion of the LMCA, competitive flow and even the steal phenomenon when two bypass grafts are used^{43,44} and retrograde perfusion of an extensive myocardial area when only one bypass graft is constructed.⁴⁵ Direct surgical angioplasty is another option for ostial disease.⁴⁶ However it is less preferred now a days due to lack of experience and technically more challenging.⁴⁷ Theoretical advantages of surgical angioplasty over CABG include restitution of normal blood flow through the LMCA providing antegrade perfusion to the entire coronary vasculature, avoiding competitive flow, saving conduits in young patients for future use and ensuring the left main stem remains patent facilitating later PCI.⁴⁶ Nowadays PCI with drug eluting stents (DES) has become alternative treatment to CABG in patients with isolated LMCA ostial disease.⁴⁸ These patients belong to low SYNTAX score (<22)⁴⁹ category. In SYNTAX trial,⁴⁸ results from left main subgroup analysis showed that the major adverse cardiac and cerebrovascular events (MACCE) were similar between CABG and PCI group in patients with low (p=0.33) and intermediate (p=0.90) SYNTAX score at 3 years. PRECOMBAT trial⁵⁰ also showed non-inferiority of PCI to CABG for the primary composite endpoint of MACCE at 5 years. Recently published EXCEL trial⁵¹ also demonstrated that in patients with low and intermediate Syntax scores PCI is non inferior to CABG for MACCE at the end of 3 years. However NOBLE trial⁵² showed that CABG might be better than PCI in patients with unprotected LMCA disease. In our study 21(75%) patients with isolated LMCA ostial disease underwent PCI with DES. There was no peri-procedural, immediate, short term or 1 year mortality. In non-ostial group 25 (8.3%) patients underwent PCI. This study was not powered to analyze the effect of CABG and PCI on outcome of patients with isolated LMCA ostial disease, though we found no difference in 1 year mortality indicating both treatment modalities can be implemented successfully.

6. Study limitations

The study population was relatively small, though larger than previous studies. The diagnosis of significant LMCA ostial disease was purely based on angiogram findings. The visual estimation of the left main lesion by angiography has considerable inter observer and intra observer variation. Studies have reported that angiographic determination of the degree of LMCA stenosis may be underestimated in as many as 71% of cases. However to improve the accuracy we used 4 experienced angiographers. Utilization of adjunctive tools like Intravascular Ultrasound will enhance the diagnostic accuracy in evaluating lesions of uncertain severity especially in LMCA. Also angiographic follow up was not performed. The population was very heterogeneous and follow up methods differed. Most patients had exercise tests while others had only clinical or telephonic follow up.

7. Conclusions

Isolated LMCA ostial disease is a rare variant of LMCA disease that is more common in middle aged females compared to non-

ostial LMCA disease which is common in older males. These patients have few coronary risk factors and normal LV function with normal regional wall motion. However, mortality is same between the two groups, independent of the treatment offered. The clinical and angiographic profile of these patients suggests that this group may represent a distinct clinical entity. Cardiologists need to be aware of this rare condition so that early diagnosis can be made and effective treatment is given, in order to improve the prognosis in these patients. Further large scale studies need to be done to evaluate the cause for different mode of presentation of this rare disease.

Conflict of interest

No conflict of interest involved in the study.

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