

Coronary artery disease and mesenteric artery stenosis - Two sides of the same coin? - Long term prospective analysis

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Summary

Coronary artery disease (CAD) patients might have concomitant mesenteric artery stenosis (MAS). Identification of risk factors predicting mesenteric artery involvement might guide screening high risk individuals. A dilemma of intervention in radiologically severe MAS exists. This prospective study included CAD patients undergoing a coronary angiogram. A concomitant mesenteric angiogram was performed to diagnose MAS. Clinically relevant MAS (CR-MAS) was defined as *i*) presence of classical mesenteric angina with any degree of MAS or *ii*) severe stenosis (> 70%) involving two or more vessels. Risk factors for CR-MAS were studied and followed up prospectively. One hundred and three patients were included in the study. Left anterior descending artery was the most common involved coronary artery and was affected in 73% ($n = 76$). Mesenteric angiogram revealed 42.7% ($n = 44$) to have MAS. CR-MAS was present in 21 patients (20.4%). Involvement of celiac axis, superior mesenteric artery and inferior mesenteric artery was 22, 39 and 15 respectively. Multivariate analysis showed mesenteric angina ($p < 0.01$), diabetes mellitus ($p < 0.01$) and peripheral artery disease ($p < 0.01$) to be independent predictors of CR-MAS. At a median follow-up of 36 months (range 29-48 months), there was no acute mesenteric ischemia. In patients with CR-MAS, 16 (76.2%) had symptomatic improvement and 5 (23.8%) had stable symptoms. Three patients underwent angioplasty of superior mesenteric artery for persistent symptoms. Chronic CAD patients had a high prevalence of MAS. Mesenteric angina, diabetes mellitus and peripheral artery disease are independent predictors of CR-MAS. Intervention for MAS should be dictated by symptoms and not radiological severity. Lifestyle modification and medication for atherosclerotic ischemic heart disease probably prevents acute mesenteric ischemia in CAD patients.

Keywords: Mesenteric ischemia, coronary artery disease, angiography, chronic mesenteric ischemia, mesenteric artery stenosis

1. Introduction

Stenosis or occlusion of the mesenteric arterial circulation is the predominant causative factor of chronic mesenteric ischemia (CMI) (1). While acute mesenteric ischemia has a dramatic presentation, CMI has an insidious course (2). The natural course of CMI is gradual with non-specific abdominal pain and

unremarkable physical findings. Hence diagnosis of CMI is often delayed by months or even years (3).

Atherosclerosis is the leading cause of CMI (3,4). The process of atherosclerosis is a generalized process affecting all vascular beds (such as renal artery, coronary artery, peripheral artery *etc.*) (5). However, variability of sequence and severity of affectation at various sites exists. Numerous studies have demonstrated asymptomatic arterial narrowing in vascular territory during evaluation of symptomatic lesions involving another region (6,7).

Limited prospective data exists regarding mesenteric arterial stenosis (MAS) (5,8,9). Asymptomatic MAS

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has been studied during evaluation of arterial occlusion at distant sites. While Thomas *et al.* (8) showed that 6% of patients with asymptomatic mesenteric artery stenosis (MAS) developed mesenteric ischemia during a mean follow up period of 2.6 years, other studies have reported no incidence of acute mesenteric ischemia despite radiological MAS (5,9). Thus, management of asymptomatic yet significant MAS is controversial.

On the other hand, MAS with mesenteric anginal symptoms or narrowing of two or more of the three mesenteric arteries are considered for revascularization (4,10). The rationale is based on the assumption that these patients are more likely to have acute mesenteric ischemia.

The incidence of MAS in ischemic heart disease has not been studied before. Incidence is likely to be high given that 33% of patients undergoing surgery for CMI have coronary artery disease (CAD) (11). We believe that CAD is likely to be associated with MAS given the universal nature of the atherosclerotic process. The non-specific abdominal symptoms of CMI make it difficult for the physician to differentiate from other more common causes like drug induced gastritis. Lack of reliable non-invasive investigation to accurately identify CMI compounds the difficulty. Possible identification of risk factors for MAS in CAD patients might help in risk stratification and guide appropriate management. We also wanted to study the course of asymptomatic MAS and clinically relevant MAS (CR-MAS) on medical management.

Thus, we decided to prospectively study the incidence and predictive risk factors for CR-MAS in CAD patients. The natural course of patients with asymptomatic mesenteric involvement and CR-MAS was also studied.

2. Patients and Methods

A prospective study of patients with suspected chronic stable angina admitted for coronary angiogram in the Department of Cardiology from January 2013 to June 2014 was done. Institutional ethics committee approval was obtained. After obtaining informed consent, patients were enrolled for the study.

2.1. Criteria for suspecting chronic stable angina

Canadian Cardiovascular Society (CCS) class III angina on maximal medical treatment for minimum period of 3 months (12).

2.2. Exclusion criteria

The exclusion criteria were *i*) age < 18 years; *ii*) patients with normal coronaries on angiogram; *iii*) Mehran risk score (13) > 5 for contrast induced nephropathy.

A detailed history was taken, with emphasis on the risk factors for atherosclerosis and abdominal

symptoms was done followed by complete clinical examination. Allen test was performed to confirm the patency of the palmar arches.

Mesenteric angina was defined as abdominal pain occurring after 15-60 minutes following ingestion of a meal and may last from 1-4 hours (3).

Patients were subjected to basic investigation including renal parameters. Echocardiogram was performed as a part of cardiac evaluation. Risk stratification for contrast induced nephropathy was done based on the Mehran Risk Score (13).

2.3. Procedure for angiogram

Pre-procedure hydration was maintained by administration of intravenous fluids. Right radial artery was the preferred site of catheterization. Catheterization was done by Seldinger technique and coronary study was performed in the usual way. If coronary arteries were involved, then mesenteric angiogram was done by selective cannulation of the three mesenteric arteries performed in two views - antero-posterior and lateral views. If selective cannulation could not be obtained, the non-selective study was performed by pressure injection using a pigtail catheter. After the procedure, a compression dressing was applied. During the procedure, patient ECG, pressure and oxygen saturation was continuously monitored. Patient was monitored for anaphylactic reaction. Patients were discharged after 24 hours. If therapeutic intervention was planned, it was performed after 3 days.

2.4. Grading of severity of stenosis

i) Normal – 0-30% narrowing of mesenteric vessel; *ii*) Mild stenosis – any degree of narrowing without fulfilling the criteria for severe stenosis; *iii*) Severe stenosis – any one of the below: $\geq 70\%$ narrowing; any degree of narrowing with post stenotic dilatation or presence of collaterals.

2.5. Criteria for clinically relevant MAS

Clinically relevant MAS was defined as any degree of narrowing of mesenteric vessel(s) with at least one of the following conditions (10): *i*) presence of classical mesenteric angina with any degree of MAS; *ii*) severe stenosis involving two or more vessels.

2.6. Management of specific conditions

i) Coronary artery disease: As per our institute protocol, only diagnostic angiogram is performed in chronic stable angina at first sitting. Therapeutic angioplasty and bypass surgery were advised as indicated.

ii) Mesenteric artery disease: Patients with CR-MAS

were assessed and offered mesenteric revascularization after management of CAD. All patients, including patients without MAS initially, were questioned about history of mesenteric angina and clinically examined. Re-evaluation of mesenteric arteries (ultrasound doppler or computed tomography) during follow up was done in cases of new-onset symptoms.

Medical management (lifestyle medication, control of co-morbid disease, antiplatelet, statins) was instituted in patients with any degree of MAS including those with CR-MAS who refused intervention (10). Patients with persistent abdominal anginal symptoms despite medical management for 6 months were advised to have endovascular or surgical intervention.

iii) Peripheral vascular disease: Symptomatic individuals with critical limb ischemia were advised to have revascularization (endovascular or surgical bypass). Amputation at appropriate level was advised for non-salvageable limb or non-reconstructible lesions with critical limb ischemia.

2.7. Follow up

Patients were followed up every 6 months. Thorough clinical examination including history of abdominal symptoms was done. ECG and echocardiogram were done every 6 and 12 months respectively. Intervention was performed as per the indication mentioned above. Medical co-morbidities were assessed and treated accordingly. All patients were advised about lifestyle modification and diet as per the AHA Diet and Lifestyle modification Recommendation: Revision 2006 (14). These included: Maintaining healthy body weight; Diet rich in vegetables, fruit, whole grain, high-fiber foods; Restricting salt intake (< 6 grams/day); Avoiding usage and exposure to tobacco in any form; Minimizing beverages and food with added sugars; Limiting intake of saturated fat.

2.8. Statistical analysis

Data was entered and analysis was performed using the Statistical Package for the Social Sciences (SPSS for Windows, Version 22.0; SPSS Inc, Chicago, Ill). χ^2 or Fisher's exact test was used for univariate comparison; continuous variables were analyzed by using the unpaired Student's t test. Multivariate logistic regression analysis of factors significant on univariate analysis was performed to identify predictive risk factors for CR-MAS. All *p* values less than 0.05 were considered statistically significant.

3. Results

From January 2013 to June 2014, a total of 110 patients underwent coronary angiogram for suspected ischemic heart disease in the Department of Cardiology. Seven

patients had a normal coronary study. Thus, one hundred three patients were included for further analysis.

3.1. Demographic features

The mean age of the population under study was 56.31 years. Sixty-six patients were male (64.1%). Comorbidities were present in 82 patients (79.6%). The incidence of diabetes, hypertension, previously diagnosed ischemic heart disease, peripheral arterial disease and dyslipidemia was 39.8%, 22.3%, 22.3%, 20.4% and 31.1% respectively. Twenty-six (25.2%) patients had mesenteric angina. The classical triad of mesenteric angina, sitophobia and weight loss was present in only 2 patients. Table 1 describes the demographic features of the study population.

3.2. Coronary artery disease

With respect to the coronary arteries the prevalence of single vessel, double vessel and triple disease was 36% (*n* = 37), 43% (*n* = 44) and 21% (*n* = 22), respectively. Left anterior descending artery was the most common involved coronary artery and was affected in 73% (*n* = 76) of the study population. Isolated left anterior descending artery affection was present in 19 patients with isolated left circumflex and right coronary artery involvement in 14 and 5 patients respectively. Table 2 depicts the distribution and severity of coronary artery involvement.

3.3. Mesenteric vascular disease

Mesenteric angiogram revealed 42.7% (*n* = 44) to have MAS. Twenty-one (20.4%) patients had CR-MAS (19 – mesenteric angina with any degree of MAS; 2 – severe stenosis of two or more mesenteric arteries). The prevalence of single vessel mesenteric disease and multivessel disease among the study population was 19.4% (*n* = 20) and 23.3% (*n* = 24), respectively. All lesions were ostio-proximal in location (Figure 1). Table 2 depicts the distribution and severity of mesenteric artery involvement. One patient had a concomitant abdominal aortic aneurysm (Figure 2).

Stenosis of superior mesenteric artery was present in 89% (*n* = 39) of those with mesenteric involvement and 38% of the study population. Of these 39, isolated superior mesenteric artery stenosis was present in 16 (41%) patients. The next common artery to be involved was celiac axis followed by inferior mesenteric artery in 22 (21.4%) and 15 (14.6%) patients respectively. Severe triple vessel stenosis was present in 8 (7.7%) patients.

3.4. Risk factors for mesenteric artery involvement

The mean age of patients with and without mesenteric vessel involvement was 60.63 years and 53.08 years

Table 1. Demographic Characteristics of study population

Items	Study population (n = 103)	Mesenteric vascular disease (n = 44)	No Mesenteric vascular disease (n = 59)	p Value
Age	56.31 ± 10.4	60.6 ± 10.9	53.0 ± 8.7	< 0.01
Gender (M/F)	66/37	24/20	42/17	0.82
Mesenteric angina (Y/N)	26/77	19/25	7/52	0.01
Diabetes Mellitus (Y/N)	41/62	29/15	12/47	< 0.01
Hypertension (Y/N)	23/80	10/34	13/46	0.93
Known Ischemic heart Disease (Y/N)	23/80	13/31	10/49	0.13
Peripheral Arterial Disease (Y/N)	21/82	19/25	2/57	< 0.01
Dyslipidemia (Y/N)	32/71	15/29	17/42	0.56
Family History (Y/N)	16/87	6/38	10/49	0.65
Smoking (Y/N)	40/63	20/24	20/39	0.23
Alcohol (Y/N)	33/70	14/30	19/40	0.96
BMI (Underweight/Normal/Overweight)	8/46/49	6/29/9	2/17/40	< 0.01
Waist/Hip ratio	8/56/39	7/30/7	1/26/32	< 0.01

BMI, body mass index.

Table 2. Severity of involvement of Coronary and Mesenteric artery stenosis

Items	RCA involvement	LAD involvement	LCX involvement	Celiac Axis involvement	SMA involvement	IMA involvement
No involvement	51	27	40	81	64	88
Mild disease	22	32	28	16	18	13
Severe disease	30	44	35	6	21	2

IMA, inferior mesenteric artery; LAD, left anterior descending artery; LCX, left circumflex artery; RCA, right coronary artery; SMA, superior mesenteric artery.

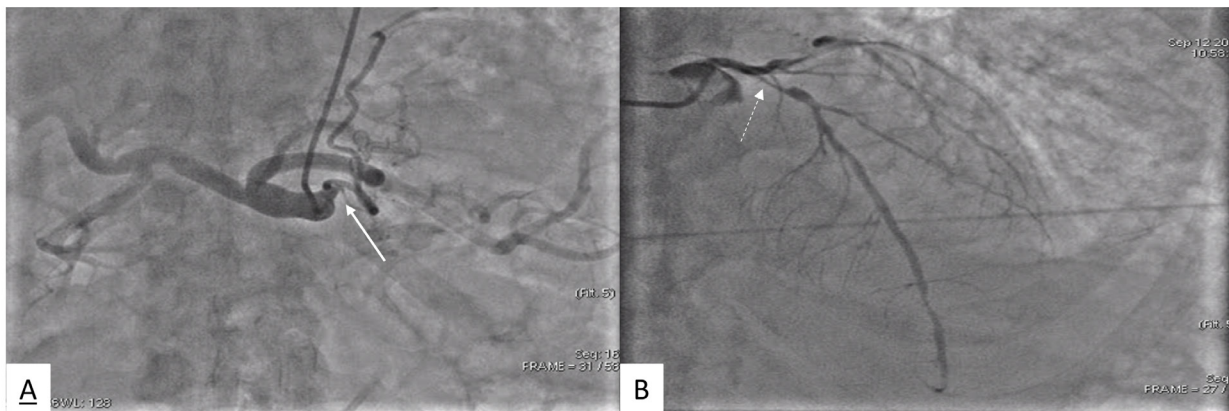


Figure 1. Conventional coronary and mesenteric angiogram. (A) Critical Celiac axis stenosis with post-stenotic dilation; (B) Left anterior descending artery ostio-proximal critical lesion with distal LAD involvement in the same patient.

respectively. Seven out of 26 patients with mesenteric angina had no evidence of mesenteric vascular disease. Nineteen and twenty-five patients had symptomatic and asymptomatic MAS respectively. Among those with MAS, 70% were diabetic and 43% had prior history of peripheral arterial disease. Comparison of clinical and biochemical parameters between group 1 and group 2 is depicted in Table 1.

Presence of MAS was not associated with the number of coronary arteries involved. However, involvement

of left anterior descending artery was significantly associated with presence of MAS ($p = 0.04$).

Univariate analysis revealed age greater than 65 years, abdominal symptoms, BMI, serum albumin, ESR, diabetes mellitus, peripheral artery disease, prior ischemic heart disease, and left anterior descending artery involvement to be significant predictor of CR-MAS. Multivariate analysis of significant factors showed presence of abdominal symptoms ($p < 0.01$), diabetes mellitus ($p < 0.01$) and peripheral artery

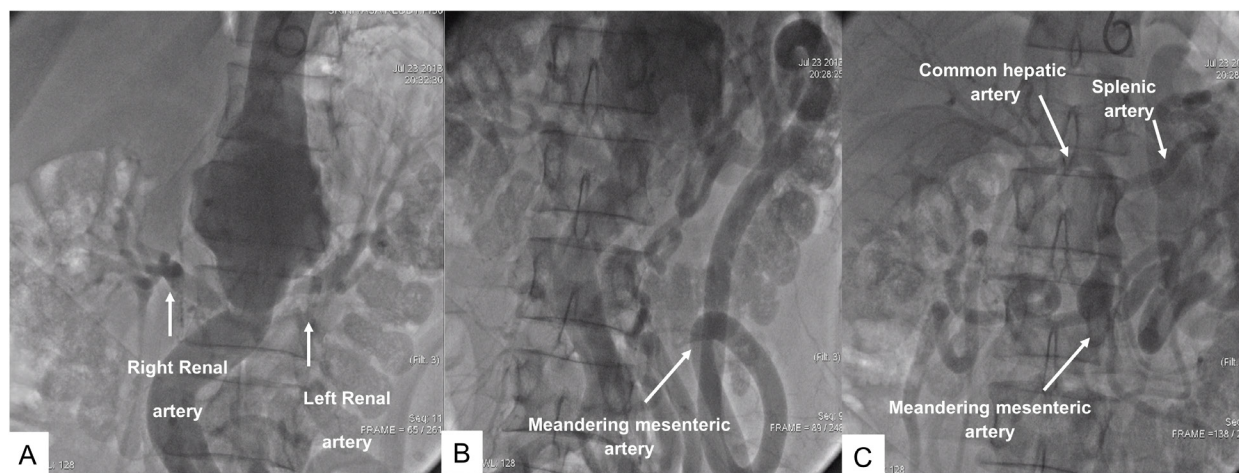


Figure 2. Photo panel of conventional angiogram of a patient with concomitant abdominal aortic aneurysm (AAA). (A) AAA with Complete occlusion of Celiac axis and superior mesenteric artery origin. Severe bilateral renal artery stenosis also noted - Lateral View; (B) Dilated Collateral (Meandering mesenteric artery) arising from Inferior Mesenteric Artery; (C) Retrograde filling of Celiac Axis and Superior Mesenteric Artery.

Table 3. Multivariate Regression Analysis for risk factors predicting CR-MAS in CAD patients

Items	Regression Coefficient	Relative Risk	95% CI	p value
Age > 65 years	1.106	3.024	0.51 - 17.87	0.222
Mesenteric Angina	2.365	10.645	1.79 - 63.27	0.009
Diabetes Mellitus	2.174	8.796	1.98 - 38.89	0.004
Peripheral Vascular Disease	3.105	22.307	2.93 - 169.53	0.003
BMI < 18.5	1.678	5.357	0.35 - 80.72	0.225
W/H ratio	2.922	18.583	0.69 - 497.74	0.082
Erythrocyte Sedimentation Rate	0.090	0.914	0.19 - 4.20	0.908
Serum Albumin	0.868	0.420	0.06 - 2.58	0.349
Left anterior descending artery involvement	1.214	3.368	0.67 - 16.84	0.140

BMI, body mass index; W/H, waist/hip.

disease ($p < 0.01$) to be independent predictors of CR-MAS (Table 3).

3.5. Follow up

Among the 103 patients, 75 individuals required percutaneous intervention and 12 others required coronary artery bypass surgery for coronary revascularization. All twenty-one patients who were advised mesenteric revascularization at index presentation refused intervention for mesenteric disease.

At the end of 36 months of median follow up (range 29-48 months), there were 12 deaths. All were related to acute coronary syndrome. Among the remaining 91 patients, 38 had mesenteric vessel involvement during the index angiogram.

Of the 21 patients with CR-MAS, 16 had improvement in abdominal symptoms, and 5 had stable symptoms. Patients with improved abdominal pain also had weight gain. Three patients out of the five with persistent symptoms underwent angioplasty for an isolated SMA lesion. There was no procedure related complication. All

three had good symptomatic relief in the form of pain relief and weight gain at median follow up of 13 months (6-15 months).

One patient with initially asymptomatic MAS developed symptoms of mesenteric angina at 2 years of follow up. He refused evaluation of the mesenteric anginal symptoms and was managed conservatively.

Major vascular events during follow-up in patients with MAS are summarized in Figure 3.

4. Discussion

Significant proportion of CAD patients had MAS (42.7%). The high prevalence of mesenteric disease, in comparison with previous studies, might be due to the variability in defining and diagnosing mesenteric artery disease (15). It is possible that angiogram, the gold standard in vascular imaging, could have detected mild stenosis missed by other imaging modalities. In order to further ascertain the individuals who might require active follow-up or intervention, we identified these clinically relevant lesions based on criteria laid out for the need

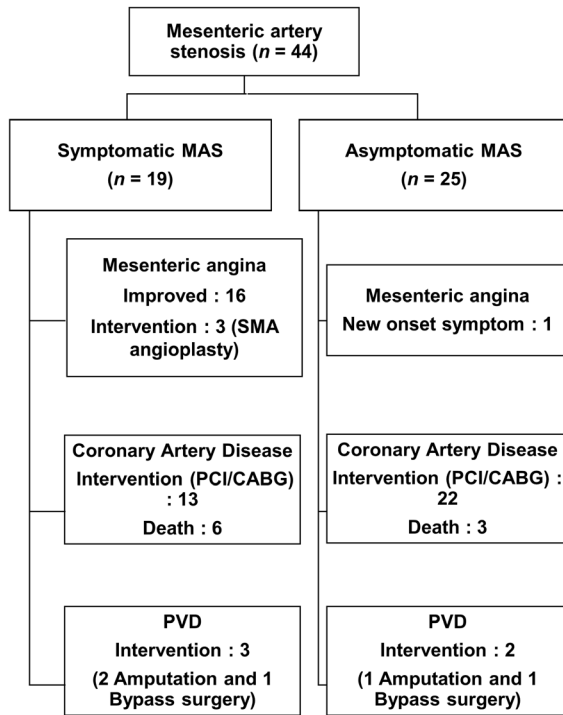


Figure 3. Flowchart depicting the major vascular events in the follow-up period in MAS patients.

for revascularization (10). The incidence of clinically relevant MAS was 20.4%. Known risk factors of the atherosclerotic process like advanced age and diabetes mellitus predicted CR-MAS (16). Increased risk of MAS in CAD patients with peripheral arterial disease highlights global involvement of the atherosclerotic process in this subgroup of individuals.

Among CR-MAS, 16 patients had symptomatic improvement and only 5 patients had persistent symptoms. Multiple factors might be responsible. Attention to coronary artery involvement is usually given priority. By the time stabilization is achieved, patients might get adapted and also alter their eating habits (17). The progression of the atherosclerotic process is also likely to be reduced given the considerable overlap of medical management of coronary artery disease and mesenteric artery disease.

The course of CR-MAS on medical management also exemplifies the controversies involved in their management. Some authors recommend intervention if patient is symptomatic or having significant involvement of two or more arteries (10). We did not have acute mesenteric ischemia in 21 patients and only 3 patients (14.2%) underwent intervention. Consideration has to be given to the degree of nutritional compromise, and number and severity of comorbidities these patients already suffer from. Given the morbidity of surgery and good proportion of CR-MAS that had symptomatic improvement, we believe that a trial of medical management has to be given before intervention is contemplated. Thus, symptoms of MAS should dictate

intervention and not radiological findings.

Advances in endovascular techniques, expertise and stents have seen the gap between a morbid open revascularization and relatively safe endovascular revascularization being narrowed (18). Though the long term outcome of severe multivessel disease is better with surgical revascularization, endovascular intervention has an important role in single vessel disease (19). The superior mesenteric artery is considered as the primary culprit for the symptoms (20). It was also the most involved artery in our study. The possibility of addressing the ostio-proximal superior mesenteric artery lesions alone may be adequate in treating symptoms, like in three of our patients, thus making an endovascular approach more attractive in this subgroup (21).

Though new onset or worsening mesenteric angina was seen, acute mesenteric ischemia was not seen at 3 years of follow up. Contradictory results in the incidence of acute mesenteric ischemia during follow up of MAS have been reported (5,8,9). We believe that strict adherence to a healthy lifestyle with antiplatelet agents and statins reduce the progression of atherosclerosis allowing time for rich collateral formation. Goals of lifestyle modification were consuming a healthy diet and achieving healthy body weight. Apart from ensuring normal blood pressure, glycemic control and correcting dyslipidemia, being physically active was stressed (14). Educating the CAD patients about the possibility of concomitant MAS is also important to ensure timely recognition and intervention.

There were limitations to our study. Patients who had symptoms of mesenteric angina but no MAS might have other causes of abdominal pain like biliary colic or gastritis. Investigations to rule out such conditions were not performed. Biochemical tests for mucosal ischemia and endoscopy to rule out drug induced gastritis could have made the diagnosis of mesenteric ischemia more specific. Similarly, repeat contrast study of patients who worsened could have identified the status of mesenteric arteries.

5. Conclusion

Significant proportion of CAD patients have MAS. Nearly one-fifth of CAD patients have CR-MAS. Mesenteric angina, diabetes mellitus and peripheral artery disease are independent predictors of CR-MAS. Intervention for MAS should be dictated by symptoms and not radiological severity. Lifestyle modification and medication for atherosclerotic ischemic heart disease probably prevents acute mesenteric ischemia in CAD patients.

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