Evaluation of mesenteric artery disease in patients with severe aortic valve stenosis

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ABSTRACT

The aim of this study is to evaluate the mesenteric artery stenosis (MAS) in routinely performed CT angiography (CTA) of patients with severe aortic stenosis (AS) planned for transcatheter aortic valve implantation (TAVI) before the procedure. Patients with AS (AS group) who routinely underwent CTA before the TAVI procedure due to severe AS and patients who had CTA for other indications (control group) were retrospectively and sequentially scanned. The demographic characteristics of the patients in both groups were similar. Calcification and stenosis in the mesenteric arteries were recorded according to the localization of celiac truncus, superior mesenteric artery (SMA) and inferior mesenteric artery (IMA). Class 0–3 classification was used for calcification score. Stenoses with a stenosis degree ≥50% were considered as significant. A total of 184 patients, 73 patients with severe AS and 111 control groups, were included in the study. SMA and IMA calcification scores of patients with AS were significantly higher than the control group (p=0.035 for SMA and p=0.020 for IMA). In addition, the rate of patients with significant MAS in at least 1 artery (45.2% vs 22.5%, p=0.001) and the rate of patients with significant stenosis in multiple arteries were also significantly higher in the AS group (8.2% vs 1.8%, p=0.037). According to the study results, patients with AS are at a higher risk for MAS. Chronic mesenteric ischemia should be kept in mind in patients with AS who have symptoms such as non-specific abdominal pain and weight loss.

Significance of this study

What is already known about this subject?

- Mesenteric ischemia is a rare but serious condition with high mortality rate.[1] The most common mechanism in acute cases is acute mesenteric ischemia associated with embolism. In chronic cases, mesenteric artery stenosis (MAS) associated with atherosclerosis is more common.
- Aortic stenosis (AS) is the most common type of heart valve disease in advanced age, also morbidity and mortality are quite high in symptomatic cases. The most frequent cause in adults is senile calcification.
- Previous studies have shown that both coronary artery disease and peripheral artery disease are more frequent in the AS population.

What are the new findings?

- We noticed that abdominal pain complaints were common in patients hospitalized for severe AS in our clinic. In the light of these observations, we thought that the incidence of atherosclerotic stenosis would be higher in mesenteric arteries in patients with severe AS and these patients might be more symptomatic due to low flow.
- As far as we can scan, the relationship between severe AS and MAS has not been reported in the literature previously.
- In our study, the rate of patients with significant stenosis in at least 1 mesenteric artery, the rate of patients with significant stenosis in multiple vessels, and the degree of stenosis in the superior mesenteric artery and inferior mesenteric artery were significantly higher in the AS group.

INTRODUCTION

Mesenteric ischemia is a rare but serious condition with high mortality rate.[1] The most common mechanism in acute cases is acute mesenteric ischemia associated with embolism. In chronic cases, mesenteric artery stenosis (MAS) associated with atherosclerosis is more common.[2] MAS is frequently asymptomatic due to extensive collateral network within the mesenteric vasculature. Despite that, patients with multiple stenoses and an underlying circulatory disorder such as heart failure may have lower symptom thresholds.[3] Aortic stenosis (AS) is the most common type of heart valve disease in advanced age, also morbidity and mortality are quite high in symptomatic cases.[4]

The most frequent cause in adults is senile calcification. AS has pathophysiological mechanisms similar to those of atherosclerosis which involve endothelial damage, lipid accumulation, calcification, inflammation and similar risk factors. Studies have shown that both coronary artery disease and peripheral artery disease are more frequent in the AS population.[5 6] We noticed that abdominal pain complaints were common in patients hospitalized for severe AS in our clinic. Moreover, we detected severe superior mesenteric artery (SMA) stenosis in 2 of these patients, and it was successfully treated

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Significance of this study

How might these results change the focus of research or clinical practice?

- In this report, the increased calcification and stenosis rate in the mesenteric arteries of an elderly and comorbidized patient group with severe AS planned for transcatheter aortic valve implantation is presented. In patients with AS, which causes a decrease in cardiac output, concomitant MAS may be the possible cause of abdominal pain, weight loss or some non-specific symptoms encountered in these patients.

percutaneously. In the light of these observations, we thought that the incidence of atherosclerotic stenosis would be higher in mesenteric arteries in patients with severe AS and these patients might be more symptomatic due to low flow. In the present study, routine CT angiography (CTA) of patients planned for transcatheter aortic valve implantation (TAVI) due to severe AS was scanned and MAS was evaluated.

MATERIALS AND METHODS

Study design and patient population

Our study was planned as a single-center, retrospective, randomized and sequential patient recruitment basis. Between 2017 and 2020, patients with aortic valve stenosis (AS group) who underwent routine CTA due to severe AS before TAVI procedure and the patients who had CTA for other indications (control group) were scanned.

Patients under 65 years of age, and those with bicuspid aortic valve, rheumatic aortic valve, hypertrophic obstructive cardiomyopathy, supravalvular AS, acute mesenteric ischemia, acute abdomen, aneurysm or dissection in the abdominal aorta, aneurysm or dissection or variation in celiac trunk (CT) or SMA, patients with no echocardiography within 1 year and patients with insufficient quality of examination were excluded from the study.

Demographic data such as gender, age, creatinine level, diabetes mellitus and dyslipidemia were recorded for each patient. Antihyperlipidemic drug use or disorder in one of the lipid values was accepted as dyslipidemia.

Image acquisition

Multidetector CTA was performed on a 64-row multidetector CT scanner (LightSpeed 64 General Electric Discovery CT750HD 2015, Milwaukee, Wisconsin, USA) with 120 kV, 300 mA, 0.98 pitch value and table speed of 64 mm per rotation. After Optiray (Dublin, Ireland), which is a 100 mL non-ionic contrast agent, was given at 3.5 mL/h, arterial phase images with a cross section thickness of 0.625 mm were obtained from the subdiaphragmatic area to the superficial femoral arteries in the 25th second.

CTA data were analyzed independently by 2 radiologists on coronal, sagittal and axial planes using OSIRIX LITE V.3.8.1 (Geneva, Switzerland) program at the workstation.

CT analysis

CT, SMA and inferior mesenteric artery (IMA) stenosis rate and degree of calcification were determined in all CTA series. Arterial diameters were measured in the normal (a) and narrowest (b) lumens. The percentage of stenosis was calculated using the North American Symptomatic Carotid Endarterectomy Trial formula ($s=(a-b)/a\times100$). At least 50% stenosis was considered as significant stenosis.

All CTAs were evaluated for calcification by the same radiologists. For this purpose, a calcification grading specific to our study was developed based on the scoring system used by van Rossum *et al*[7] (table 1).

Table 1 The classification of arterial calcification

Degree	Distribution and size of calcification
Class 0	Absent
Class I	Single focus <5 mm and <5 foci calcification
Class 2	Single focus 5–10 mm or single focus <5 mm and ≥6 foci calcification
Class 3	Single focus >10 mm or 5–10 mm multifocal calcification

Statistical analysis

Statistical analysis was carried out using SPSS for Windows V.15.0. Descriptive statistics were given as mean, SD, frequency, and percentage. The Kolmogorov-Smirnov test was used to evaluate whether continuous variables were normally distributed. An independent samples t-test was used to compare mean values between the 2 groups, and X^2 test was used for comparison of categorical data. Correlation between any 2 data was tested with the Spearman correlation analysis. Before this analysis, logarithmic transformation was applied on variables without normal distribution. Values of $p<0.05$ were considered statistically significant.

RESULTS

A total of 246 patients (104 in the AS group and 142 in the control group) were enrolled in the study according to inclusion criteria. After exclusion criteria were applied, 184 patients were included for further analysis (73 in the AS group and 111 in the control group).

The demographic characteristics of the AS group and the control group were similar in terms of age (80.4±6.7 vs 79.2±5.8, p=0.194), gender (54.8% vs 55% female, p=0.983), diabetes mellitus (21.9% vs 15.3%, p=0.253), dyslipidemia ratios (38% vs 42.9%, p=0.523) and creatinine levels (1.35±1.08 mg/dL vs 1.19±0.75 mg/dL, p=0.252).

The comparison of CT, SMA and IMA calcification scores showed that the CT calcification score was statistically similar in the AS and control groups (p=0.148). In contrast, class 3 calcification was never detected in the control group, while it was present in 3 patients of the AS group (p=0.061). SMA and IMA calcification scores were significantly higher in AS group (p=0.035 for SMA and p=0.020 for IMA). In a more detailed analysis of calcification scores, there was a more significant difference in class 3 calcification (p=0.061 for CT, p=0.007 for SMA, p=0.031 for IMA) (table 2).

The prevalence of significant stenosis (≥50%) in at least 1 mesenteric artery and in 2 or 3 mesenteric arteries (multiple) among the study population was 31.5% (n=58) and 4.3% (n=8), respectively. The rate of patients with MAS in at least 1 artery (45.2% vs 22.5%, p=0.001) and in

Table 2 Distribution of the calcification in the mesenteric arteries

	Aortic stenosis n=73	Control n=111	P value
CT calcification score			0.148
0	28 (38.4)	51 (45.9)	0.194
1	37 (50.7)	54 (48.6)	0.452
2	5 (6.8)	6 (5.4)	0.458
3	3 (4.1)	0	0.061
SMA calcification score			0.035
0	21 (28.8)	43 (38.7)	0.165
1	35 (47.9)	56 (50.5)	0.739
2	9 (12.3)	10 (9)	0.469
3	8 (11)	2 (1.8)	0.007
IMA calcification score			0.020
0	54 (74)	97 (87.4)	0.020
1	14 (19.2)	14 (12.6)	0.225
2	2 (2.7)	0	0.080
3	3 (4.1)	0	0.031

CT, celiac trunk; IMA, inferior mesenteric artery; SMA, superior mesenteric artery.

multiple arteries (8.2% vs 1.8%, p=0.037) was also significantly higher in the AS group (figure 1). In addition, the rate of patients with significant MAS (≥50%) in the AS group was higher for all 3 arteries than the control group (p=0.05 for CT, p=0.025 for SMA and p=0.032 for IMA). The comparison of CT, SMA and IMA stenosis degrees among the groups revealed that CT stenosis degree was similar between the groups (p=0.322); SMA (p=0.025) and IMA (p=0.038) stenosis degrees were higher in the AS group (table 3) (figure 2). A significant positive correlation was found between the score of calcification in each artery localization and the degree of stenosis in that artery (r=0.430 for CT, p<0.001; r=0.534 for SMA, p<0.001; and r=0.486 for IMA, p<0.001).

DISCUSSION

The most common cause of AS in adults is senile calcification. It affects 2%–3% of those over 65 years of age and up to 8% of those over 85 years. Thus, its incidence increases exponentially with age.[8 9] The average age of patients with AS in our study was 80.4±6.7 years which was higher than the average age of AS in the society. The reason for

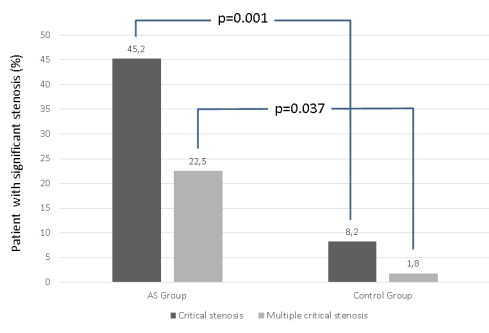

Figure 1 Distribution of patients with significant mesenteric artery stenosis (MAS) in the 2 groups by the number of affected arteries. AS, aortic stenosis.

Table 3 Properties of the mesenteric arterial stenosis in patients

	Aortic stenosis n=73	Control n=111	P value
Critical stenosis (%)	33 (45.2)	25 (22.5)	0.001
Multivessel critical stenosis (%)	6 (8.2)	2 (1.8)	0.037
CT stenosis degree	18.2±21.2	15.4±17.6	0.322
Critical stenosis in CT (%)	11 (15.1)	7 (6.3)	0.050
SMA stenosis degree	20.3±19.2	14.9±13.4	0.025
Critical stenosis in SMA (%)	10 (13.7)	5 (4.5)	0.026
IMA stenosis degree	22.3±33.4	13.1±26.0	0.038
Critical stenosis in IMA (%)	19 (26)	15 (13.5)	0.032
Total occlusion (%)	3 (4.1)	2 (1.8)	0.346

CT, celiac trunk; IMA, inferior mesenteric artery; SMA, superior mesenteric artery.

this was that the patients included in our study consisted of patients who had high risk of surgical aortic valve replacement planned for TAVI. The control group was also scanned within a similar age range. Risk factors such as age, diabetes mellitus, hypertension and dyslipidemia that would be important for the development of atherosclerosis were found similar in both groups.

Although mesenteric ischemia constitutes only 0.1% of the admissions to the hospital, it has high mortality rate (21%–94%).[1 10] In autopsy series, the reported range of mesenteric disease rates is from 30% to 80%.[11 12] Atherosclerotic stenosis of the mesenteric arteries can lead to both chronic mesenteric ischemia and acute ischemia complicated by thrombosis. In 2 studies using duplex ultrasonography, significant MAS was detected in 17%–18% of patients over 65 years of age.[13 14] In our study, this rate was found to be 31.5%. In another analysis made in patients whom renal MR angiography was performed, the rate of patients with incidental MAS was reported to be 33%.[15] This heterogeneity between studies depends on both the different patient populations and the methods used in MAS detection. Since a flow rate-based calculation is used for the measurements made with duplex ultrasonography, there may be false negativity of some anatomically important stenoses. Non-critical stenoses that do not affect the flow can be visualized with MR and CT, also additional parameters such as calcification and plaque involvement properties can be evaluated. Schaefer *et al*[16] compared digital subtraction angiography, duplex ultrasonography, CT and MR angiography methods

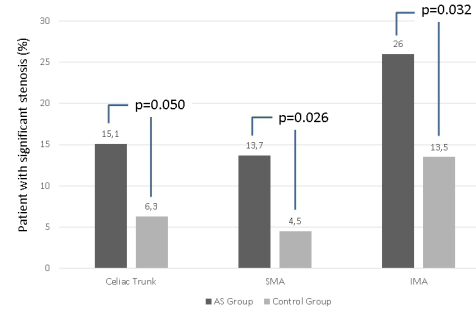

Figure 2 Distribution of patients with significant mesenteric artery stenosis (MAS) in the 2 groups according to artery localization. AS, aortic stenosis; IMA, inferior mesenteric artery; SMA, superior mesenteric artery.

in the evaluation of MAS. The researchers emphasized that the method which had the highest correlation for image quality and stenosis grading was CTA.

Plaque calcifications reflect the active phase of vascular atherosclerosis associated with inflammation. Inflammatory cytokines, such as tumor necrosis factor-α, activate osteogenic differentiation and mineralization of the extracellular matrix.[17] Especially, the relationship between intimal calcification and atherosclerosis has been demonstrated in many studies.[18–20] Moreover, calcified plaques are found to be an independent predictor of combined vascular events.[20 21] In our study, there was a significant positive correlation between calcification score and MAS degree in all 3 arteries. In addition, calcification scores in the AS group were significantly higher in SMA and IMA localization compared with the control group. In the subgroup analysis, it was observed that the degree of calcification with the most significant difference was class 3 (large or multifocal). This suggested that multifocal and large calcifications were more common in the AS group. Depending on many factors such as size, shape, distribution in the plaque and the degree of differentiation, the effect of calcification on plaque stability may vary.[18] It has been reported that multifocal calcifications increase the risk of intraplaque bleeding, provoke inflammation and trigger plaque rupture.[19 22 23] This may be due to increased surface area and biomechanical stress in the plaque because of increased number of calcifications.

As far as we can scan, the relationship between severe AS and MAS has not been reported in the literature previously. The observation that underlies the hypothesis of this study is frequent abdominal pain symptoms that we noticed in the patients whom we admitted to our clinic to perform TAVI. Moreover, severe SMA stenosis was detected in 2 of these patients and clinical improvement was achieved after treated percutaneously. It is a well-known fact that AS and atherosclerosis have similar physiopathology because they have similar risk factors. Also, histopathological changes, such as endothelial damage, inflammation and calcification, are similar. In many studies, coronary artery disease,[6 24] peripheral artery disease[25 26] and carotid artery stenosis[27] have been found to be more frequent in patients with AS. In our study, the rate of patients with significant stenosis in at least 1 mesenteric artery or in multiple vessels, and the degree of stenosis in the SMA and IMA arteries were significantly higher in the AS group. The increased atherosclerotic risk factors of patients with AS are the probable cause of this result. Studies in the literature show that mesenteric ischemia usually occurs in patients with multiple vascular disease and severe stenosis.[1 28] The reason for this is the intense collateral circulation in the mesenteric arterial bed.[3] In contrast, circulatory disorders such as hypovolemic shock, heart failure, and myocardial infarction are known to facilitate mesenteric ischemia.[2] Although not previously reported, severe AS which reduces cardiac output is a good example of promoting ischemia in an already diseased mesenteric arterial bed. In addition, impaired left ventricular systolic function may increase this risk in a significant number of these patients.

Study limitations

Our study is a retrospective study and clinical symptoms of the patients that may be associated with mesenteric ischemia have not been questioned. Therefore, the clinical reflection of the higher MAS rate in the AS group could not be analyzed in this study. In addition, although some atherosclerotic risk factors such as diabetes mellitus, hypertension, and dyslipidemia were tested, some risk factors such as smoking and heredity could not be found in most of the control group patients during file scanning. Therefore, it is not known how these factors may affect the outcome of the study. Finally, the lack of healthy individuals in the control group may have influenced the results of the study. In a study where the control group consists of healthy elderly individuals, we estimate that the results will be more significant.

CONCLUSION

In this report, the increased calcification and stenosis rate in the mesenteric arteries of an elderly and comorbidized patient group with severe AS planned for TAVI is presented. In patients with AS, which causes a decrease in cardiac output, concomitant MAS may be the possible cause of abdominal pain, weight loss or some non-specific symptoms encountered in these patients. Future prospective studies are necessary to clarify the uncertain points on this issue.

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Patient consent for publication Obtained.

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Data availability statement
Data may be obtained from a third party and are not publicly available. Image data are in the hospital database. The study data can be accessed as statistical code.

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