*TTU Journal of Biomedical Sciences 2022, **01**:29-33*
(RESEARCH ARTICLE) DOI: 10.53901/tjbs.2022.10.art05

Prolonged Coronary Transit Time and Reversed Flow Causing Functional Ischemia, Chest Pain and Syncope in Patients with Aortic Stenosis and Patent Coronary Arteries: An Angiographic and Machine Learning Analysis

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Article history: Manuscript received June 15, 2022; revised manuscript received September 15, 2022; accepted September 25, 2022.

ABSTRACT

Background. Patients afflicted with aortic stenosis (AS) may present chest pain (CP), shortness of breath (SOB), syncope, and no lesion in the coronary arteries. So far, no clear mechanism could convincingly elucidate the pathophysiology of symptoms in such patients. We conducted a study to clarify the mechanism of CP, SOB, and syncope in AS patients without coronary artery stenosis based on coronary flow patterns or abnormalities.

Methods. One hundred and thirty two (132) patients visiting the emergency room with CP, SOB, or syncope were screened for AS. Forty four (44) patients with a clinical diagnosis of AS underwent right and left heart catheterization and a novel dynamic coronary angiographic technique. Twenty AS patients without coronary artery disease (CAD) were enrolled. All patients were divided into either: group A for severe AS or group B for mild to moderate AS. The control group consisted of Five patients with normal left ventricular function without CAD nor AS (group C). The flow data included the coronary transit time duration, the presence of retrograde flow at the proximal coronary segment, and the persistence of contrast spill-out from the coronary ostium.

Results There was prolonged arterial phase and retrograde flow in the proximal coronary segment, including persistent spilling of contrast into the coronary sinus ($p<0.01$ when compared with groups B and C) in 20 patients with severe AS (group A). In 24 patients in the mild to moderate AS group (group C), there was only a moderately prolonged arterial phase without retrograde flow nor spilling of contrast from the ostium ($p=0.99$ when compared with control group C).

Conclusions In patients with AS, significantly prolonged arterial coronary transit time, reversed coronary flow, and retrograde ejection of contrast into the coronary sinus correlated statistically with the severity of AS. In patients with mild to moderate AS, with only moderate prolongation of the arterial phase without reversed coronary flow nor retrograde ejection of contrast into the coronary sinus.

KEYWORDS Aortic stenosis, chest pain, patent coronary artery, syncope, prolonged arterial phase, reversed flow, sudden cardiac death

INTRODUCTION

It is well established that patients with aortic stenosis (AS) can present with chest pain (CP), shortness of breath (SOB), and syncope despite widely patent coronary arteries and normal left ventricular (LV) ejection fraction (EF) [1]. While AS is a progressive disease, many patients remain asymptomatic until syncope or even still the point of sudden cardiac death (SCD) (which is, in fact, syncope without recovery) [2]. Previous investigations have suggested abnormalities in flow dynamics, morphological aspects, and microvascular dysfunction as culprits in the development of these symptoms [3], [4]. However, no mechanism could convincingly clarify the pathophysiology of CP, SOB, syncope or SCD in AS patients because no technique was available to illuminate that. In the past 5 years, our group has developed a new recording technique focusing on coronary flow in preference to the narrowing seen in the contrast-filled coronary lumen [5]. With the application of this new technique, our study aimed to clarify the mechanism of CP, SOB, and syncope in AS patients without coronary artery stenosis based on coronary flow patterns or abnormalities.

METHODS

Subject Enrollment

In a prospective protocol, a cohort of 132 patients who visited the emergency room from January 2019 to December 2021 with complaints of CP, SOB, or syncope was screened by echocardiography. If the non-invasive test suggested AS, the patients subsequently underwent coronary angiogram (CAG) with right and left heart catheterization. Forty four AS patients who presented without coronary lesions by visual angiographic assessment and LVEF >50% were enrolled. They were divided into 2 groups: Group A for patients with severe AS (20 patients) and group B for mild to moderate AS (twenty four patients). Severe AS was defined as an aortic valve area (AVA) of <1.0cm^2 and a left ventricular-aortic pressure (LV-AO) gradient >40mmHg, according to the guidelines of the American College of Cardiology [6]. Mild to moderate AS was defined as an AVA ranging from 1.0-1.5cm^2 and a LV-AO gradient of 20-39mmHg [6]. In the cohort of screened patients, a small group of 15 patients (<50 years of age), without AS underwent coronary angiogram for other indications. As their coronary arteries showed no lesion and their LVEF was normal without left ventricular hypertrophy or other valvular abnormalities, these patients were enrolled and served as the control (group C).

Exclusion Criteria

Patients presenting with coronary lesions at any stage were excluded because coronary artery disease (CAD) could induce CP, SOB, syncope or SCD, irrespective of the aortic valve status. The AS patients were also excluded if they had end-stage disease with survival time <6 months, or if they had other severe hemodynamic disturbances such as hypotension from non-cardiac problems (sepsis, bleeding, etc).

TABLE 1. Classification of Patients

	Severe Aortic Stenosis (group A)	Mild to Moderate Aortic Stenosis (group B)	Control (group C)
Aortic valve area	<0.7cm^2	>1.0cm^2	>2cm^2
Gradient		Normal	Normal
Coronary Lesions	None	None	None

Exclusion Criteria

Patients presenting with coronary lesions at any stage were excluded because coronary artery disease (CAD) could induce CP, SOB, syncope or SCD, irrespective of the aortic valve status. The AS patients were also excluded if they had end-stage disease with a survival time <6 months or if they had other severe hemodynamic disturbances such as hypotension from non-cardiac problems (sepsis, bleeding, etc.).

Novel Technique of Dynamic Coronary Angiography

In this study, two experienced interventional cardiologists serving as operators performed all coronary angiographies and left and right heart catheterizations based on the aforementioned new dynamic recording technique. Initially, the operators positioned the camera at an angle so that the index artery could be filmed in its entire length completely within view of the screen. The reason was that the operators needed to record all characteristics of the flow without interruption from the ostium to the distal end. While the camera was recording, the operators injected contrast until complete opacification of the index artery. As the injection concluded, the operators continued filming the blood in white color, moving in, displacing the contrast until all the contrast disappeared from the distal vasculature. The morphology, movements, and interactions of the blood flow in white color against the black background of contrast could be clearly captured, identified, and tabulated [5].

Once the angiography was completed, the coronary angiograms were uploaded to an electronic health record platform, while each coronary image (15 images per second) was saved in a PowerPoint (PPT) file. The PPT slides could be replayed at various speeds and allowed the operators to identify the details of flow, its morphology (laminar, turbulent, or stagnant), its direction (antegrade versus retrograde or standing still), intensity (from mixed black and white to completely black of contrast or white of blood), and exact duration (67 milliseconds (msec) per image, etc.) [5]. Many new minute details were discovered and documented by this reviewing technique on PPT slides, whereas they would have been missed by a cursory glance at the images of a running angiogram on a laptop or desktop. This novel technique of dynamic coronary angiography and its comprehensive review protocol was previously published [5].

Data Collection

In this study, all the senior and junior authors were well trained in the novel angiogram reviewing technique and focused on the characteristics of normal and abnormal coronary flows. The first measurement was the duration of the arterial phase (AP), or arterial coronary transit time, which was calculated from the time of the entry of the blood to the end when all the contrast disappeared from the arterial circulation. The meaning of contrast disappearance is that the blood successfully displaced and replaced the contrast in the distal vasculature. The second measurement was the presence of the retrograde flow, in which the contrast (in black) flew in a retrograde direction from the middle segment toward the proximal or ostial coronary segment. The third measured variable was the presence of the retrograde spill of contrast from the coronary ostium into the coronary sinuses of the aortic root.

Statistical Analysis

Categorical data are presented as frequency (percentage), and comparison between groups was performed using the chi-square test or Fisher exact test. The distribution of continuous variables was assessed using skewness, kurtosis, and visual inspection of the histogram. Continuous variables are presented as mean, ± standard deviation (SD), or expressed as median (interquartile range) for non-normal distribution. Differences in continuous variables between three groups were analyzed using a one-way analysis of variance (ANOVA), or Kruskal–Wallis test, as appropriate. In addition, Bonferroni correction was implemented for multiple comparisons. A two-sided p-value of <0.05 was considered statistically significant. The statistical analyses were performed using R software, version 4.0.3 (The R Foundation, Vienna, Austria).

Study Approval

The ethical committee of the University Research Consortium approved the study.

RESULTS

The demographic data of forty-four AS patients (mean age= 65, 36% female) and fifteen normal controls can be found in Table 2. The correlations between the coronary flow abnormalities with the recurrence of symptoms are presented in Table 3. The first key finding was a prolonged arterial coronary transit time in ALL patients ranging from mild to severe AS (Group A and B), with the highest level in patients of group A (p<0.01). The second key finding was the persistent retrograde flow and spilling of contrast in the coronary sinus from the ostium of the index artery in patients with severe AS (group A).

Prolonged Coronary Arterial Transit Timel

As a baseline, the control group C patients who presented with normal coronary flow, and left ventricular function without valvular abnormality, had an arterial phase of 1.55 ± 0.09 seconds. Group B patients with mild to moderate AS

TABLE 2. Demographic and Clinical Features

	Mean ± SD or N (%)
Age (years)	65 ± 3.5
Gender	
Male	60%
Female	40%
Cigarette smoking	24%
Diabetes mellitus	24%
Hypertension	48%
Anemia	08%
Dyslipidemia	48%

TABLE 3. Demographic and Clinical Features

DIAGNOSIS	Normal control (group C)	Mild to Moderate Aortic Stenosis (group B)	Severe Aortic Stenosis (group A)
Aortic valve area	3.0 cm^2	1.26 ± 0.164 cm^2	0.7 ± 0.35cm^2
Ejection Fraction	60% (by left ventriculogram)	54% (by left ventriculogram)	55% (by echocardiogram)
Duration of Arterial Phase (seconds)	1.55 ± 0.09	1.57 ± 0.21 P=0.99	(B vs C) 3.54 ± 1.14 p< 0.001 (A vs B and C)
Reversed flow with spilling in the coronary sinus	NO	NO	Present

(AVA=1.0 -1.5cm^2) presented an average arterial phase of 1.57 ± 0.21 seconds. For patients with severe AS (AVA from 1.0 cm2 to 0.6 cm^2), the prolongation of the arterial phase was pronounced and averaged 3.54 ± 1.14 seconds (p<0.01). Utilizing the Bonferroni correction for multiple comparisons, the difference was statistically significant between moderate AS vs. severe AS (p<0.001), with similar results between the control group and severe AS (p<0.001). Conversely, no difference was found between the mild to moderate AS and the control group (p=0.99).

Persisting Reversed Flow

Patients with mild to moderate AS presented no reversed flow. In contrast, the patients with severe AS had significant recurrent reversed flow in the proximal coronary segment culminating in the ejection of contrast back in the coronary sinus (Figure 1).

DISCUSSION

The objective of our study was to clarify the mechanism of CP, SOB, and syncope in AS patients without coronary artery stenosis based on coronary flow patterns or abnormalities. Primarily, the arterial phase was prolonged for all patients from mild to severe AS (groups A and B). Second, for patients with severe AS (group A) it was found that in

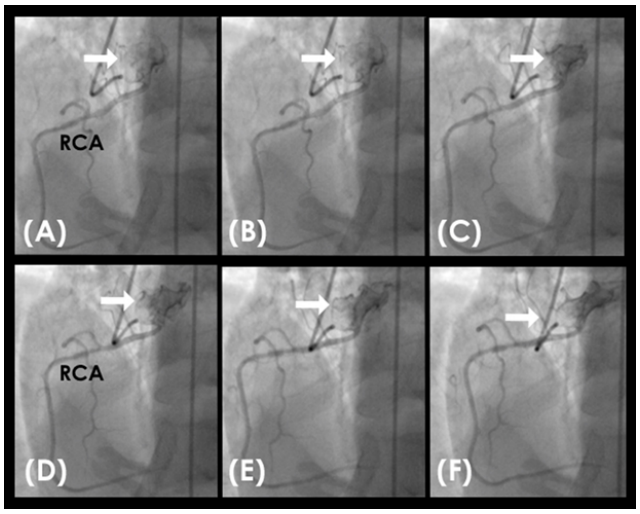

FIGURE 1. Reversed Flow in the Right Coronary Artery. This is a series of six sequential images separated by 0.067 second each (15 images per second). (A) The operator injected contrast to the right coronary artery (RCA). Because of high pressure inside the RCA, the diagnostic catheter flipped out. Contrast (black) could be seen coming out of the RCA ostium, spilling in the aortic sinus (white arrow). **(B) and (C)** The area of spillage became darker and darker because more contrast was spilling out (white arrow). **(D)** Contrast (black) could be seen coming out of the RCA ostium and spilling into the aortic sinus in a disorganized fashion (i.e., turbulent) (white arrow). **(E)** The cloud of contrast expanded (arrow). **(F)** The area of contrast became larger and darker because more contrast was spilled (arrow).

conjunction with a significantly prolonged arterial phase, the flow was reversed in a retrograde direction and culminated in a persistent ejection of contrast from the ostium to the coronary sinus in the aortic root. The arterial phase was defined as the time of blood entry at the ostium until all the contrast was replaced (pushed out) by the blood from the distal arterial system. In normal individuals with a heart rate of 60 beats per minute (BPM), the arterial phase averaged 1.55 ± 0.09 seconds, or equivalent to a delivery or renewal rate of new blood at 38.7 times (or loads) per minute. With this being understood, the arterial phase was considered a surrogate for the frequency and amount of new blood delivered to the myocardium. The delay in delivery of oxygen-rich blood to the myocardium due to an excessively prolonged arterial phase (as in group A) could spark ischemia and trigger near-fatal or fatal arrhythmias presented as CP, syncope, or SCD [1]-[3]. This is the best explanation of the mechanism which develops symptoms of CP, syncope, or SCD in AS patients and patent coronary arteries. Besides similar findings of prolonged arterial phase in the TIMI frame count and the Doppler flow technique, one unanticipated result was that our novel dynamic angiographic technique allowed for the identification and measurement of retrograde flow. The TIMI frame count could not detect the retrograde flow because the count was based on the images of antegrade injection of contrast [7]. The Doppler flow study could not detect the retrograde flow because the sensor at the tip of the Doppler wire could only measure the speed and direction of the flow at one location at a time and not of the whole length of the artery at the same time [8]. This limitation does not exist in our new dynamic angiographic technique due to it being based on real-time imaging of blood flow. This new technique could demonstrate both the presence of antegrade flow during diastole and retrograde flow during systole. The new technique can also present the possible simultaneous existence of distal antegrade and proximal retrograde flow in early systole [5]. The persisting retrograde ejection of contrast (spillover) from the coronary artery into the aortic root was the most substantial evidence of coronary constriction by the left ventricle in systole in patients with severe AS. Once AS brings about reversed flow and contrast spillover at the coronary ostium, these AS patients have recurrent symptoms of chest pain or syncope. These two new observations (reversed flow and contrast spill) also accounted for the significant severity of AS [9].

Limitations

The major strength of this study is the use of a new angiographic technique which could show the prolonged arterial phase and the presence of retrograde flow. This study also has several limitations. Primarily, this is a non-randomized observational study in which the patient's sample was small. The results are only exploratory and not confirmatory. Second, the impact of all confounding factors, such as classical risk factors, comorbidities, etc., could not be assessed. Third, a prolonged arterial phase was correlated with the symptoms of ischemia and not a direct cause-effect analysis. This study is only exploratory and a starting point for further research. A larger cohort would be needed to validate the new findings within the general population.

CONCLUSIONS

In accordance with our study, we concluded that significant prolongation of the arterial phase caused delay in delivering new blood to the myocardium and subsequently created ischemia in AS patients with patent coronary arteries. The presence of persisting reversed coronary flow, and ejection of contrast from the coronary artery to the aortic sinus represented the severity of ischemia which was found to be correlated with recurrent symptoms of chest pain and syncope.

CONFLICTS OF INTEREST

None of the authors have conflicts of interest to declare.

REFERENCES

[1] Ross JJ, Braunwald E"Aortic stenosis." Circulation, Jul. 1968, 38:61–67, DOI: 10.1161/01.cir.38.1s5.v-61, PMID: 4894151.

[2] Frey N, Steeds RP, Rudolph TK et al."Symptoms, disease severity and treatment of adults with a new diagnosis of severe aortic stenosis." Heart (British Cardiac Society), Nov. 2019, 105:1709–1716, DOI: 10.1136/heartjnl-2019-314940, PMID: 31302639.

[3] Taniguchi T, Morimoto T, Shiomi H et al."Sudden Death in Patients With Severe Aortic Stenosis: Observations From the CURRENT AS Registry." Journal of the American Heart Association, May. 2018, 7, DOI: 10.1161/JAHA.117.008397, PMID: 29776957.

[4] Kaski JC, Crea F, Gersh BJ et al.“Reappraisal of Ischemic Heart Disease.” Circulation, Oct. 2018, 138:1463–1480, DOI: 10.1161/CIRCULATION-AHA.118.031373, PMID: 30354347.

[5] Nguyen T, Chung D, Ngo L et al.“Challenges of the 21 ST Century: Part 2 - Dynamic angiography in the investigation of cavitation in coronary arteries: Standard description of coronary lesions and blood flow,” European Journal of Anatomy, 2021, 25-2025:9–28.

[6] Nishimura RA, Otto CM, Bonow RO et al.“2014 AHA/ACC Guideline for the Management of Patients With Valvular Heart Disease: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines.” Circulation, Jun. 2014, 129:2440–2492, DOI: 10.1161/CIR.0000000000000029, PMID: 24589852.

[7] Gibson CM, Cannon CP, Daley WL et al.“TIMI frame count: a quantitative method of assessing coronary artery flow.” Circulation, Mar. 1996, 93:879–888, DOI: 10.1161/01.cir.93.5.879, PMID: 8598078.

[8] Heller LI, Cates C, Popma J et al.“Intracoronary Doppler assessment of moderate coronary artery disease: comparison with 201Tl imaging and coronary angiography. FACTS Study Group.” Circulation, Jul. 1997, 96:484–490, DOI: 10.1161/01.cir.96.2.484, PMID: 9244216.

[9] Chung D, Ngo LM, Vu L et al.“No Flow In The Distal Coronary Segment And Reversed Flow At The Proximal Segment Are The Mechanisms Of Chest Pain In Patients With Aortic Stenosis And Patent Coronary Arteries,” Journal of the American College of Cardiology, 2020, 75:2158.