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Unmasking Syndrome X

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ABSTRACT

Background. The differential diagnosis of chest pain in women is complex, ranging from atypical angina to chest pain in the absence of coronary artery disease (i.e., Syndrome X). The mechanism of these conditions remains unexplained. The purpose of this study was to examine coronary blood flow based on a new angiographic technique.

Methods. Patients with chest pain were enrolled. In the new technique, as the contrast injection stopped, the blood in white color moved in and displaced the black contrast. Characteristics of blood flow could be observed and classified by types and time. The duration of the arterial phase was calculated and compared with control.

Results. Sixty patients were enrolled. Ten patients with normal coronary arteries and ventricular function; without chest pain served as controls. In the control group, the duration of the arterial phase in the RCA was 1.76 sec, while it was 3.76 sec for the syndrome X group ($p<0.05$). From the mMID segment to the distal segment, syndrome X patients had a much longer delay compared to control subjects (0.81 vs. 0.26 sec) ($p<0.05$). From the distal segment (bDIS) to the origin of the PDA, syndrome X patients had an average duration of 0.81 sec compared to 0.40 sec in controls ($p<0.05$). The largest difference was the period of time when the contrast left the PDA until flushed from the distal vasculature and was 1.66 sec and 0.40 sec in syndrome X vs. control. Syndrome X patients with prolonged myocardial phase (1.89 sec) had dense and prolonged contrast retention at the myocardium.

Conclusions. In patients with syndrome X, the prolonged arterial phase deprived the myocardium of highly oxygenated blood and triggered ischemia. This new imaging method allows for a better understanding of the mechanism of ischemia in Syndrome X patients.

KEYWORDS Atypical Angina, Coronary Artery Disease, Syndrome X

INTRODUCTION

TWomen frequently present with atypical angina pectoris (AAP) symptoms making ischemic heart disease recognition, diagnosis and treatment challenging [1]-[3]. Typical angina pectoris (TAP) defined as substernal discomfort occurring with physical exertion or emotional stress, and relieved within 10 minutes (min) by rest or nitroglycerin, is frequently used to help predict the presence of obstructive coronary artery disease (CAD) [3]. In contrast, patients with AAP present with only two of the three characteristics of TAP and a diverse range of symptoms. Further, at the end of this spectrum of presentations, patients may present with chest pain of non-cardiac origin, also known as pseudo angina pectoris (PAP) (Table 1). One form of AAP known as

Cardiac Syndrome X (CSX) is defined as angina-like chest pain with evidence of myocardial ischemia in the absence of flow-limiting stenosis on coronary angiography (CAG). Because CSX is characterized as a decrease in coronary flow reserve without epicardial artery stenosis, CSX is also referred to as microvascular angina [4], [5]. CSX is more common in women than men and occurs more frequently in peri-menopausal and postmenopausal women [6]-[9]. The mechanism(s) underlying CSX are unclear and suggested to include endothelial dysfunction, myocardial ischemia, insulin resistance, anomalous autonomic control, altered cardiac sensitivity, and estrogen deficiency [1], [6], [10]-[17]. Of these, endothelial dysfunction seems to be the prevailing theory. The objective of the present work was to examine coronary flow abnormalities using a novel, dynamic coronary angiography technique to explain the cause of angina and other symptoms in patients with CSX.

METHODS

We review our database for female and male patients hospitalized for complaint of chest pain with or without fatigue or shortness of breath (SOB) from December 2020 to June 2022. During hospitalization, all patients underwent bilateral CAG, including right and left heart catheterization.

Inclusion and Exclusion

All Patients were enrolled in this study if CAG showed patent or minimally diseased coronary arteries. A group of patients with (1) normal coronary arteries, (2) left ventricular function without valvular anomalies, and (3) a confirmed non-cardiac cause for chest pain (Table 1), served as control. Patients were excluded from this study if they had a significant valvular disease, mild to severe CAD, acute coronary syndrome, or severe critical hemodynamic problems such as hypotension from non-cardiac conditions (i.e., sepsis, bleeding, etc.).

Technique of Dynamic Coronary Angiography

The technique of coronary angiography was described in detail in prior publications [18]. In summary, coronary angiography (CAG) was performed using a novel technique requiring the angiographers to inject the contrast until the index coronary artery was completely opacified. As the injection of contrast stopped, the blood (in white color) moved in and displaced the contrast (in black color). Thus, morphologies, movements, directions, and interactions of the blood flow could be observed in white color against a black background. The angiograms were recorded from the beginning of injection until all the contrast disappeared from the distal vasculature (i.e., the arterial phase) and ended after the contrast was gone from the coronary sinus (i.e., the venous phase). During injection and afterward, a camera was positioned at an angle that could record the index artery in its full length, with all the images totally inside the screen, at 15 images per second. The angiograms were saved and stored in the EPIC Electronic Health Record System (Epic Systems Corporation, Madison, WI).

TABLE 1. Classification of Chest Pain

Anginal Classification	Description
Typical Angina (TAP) (aka, Definite Angina)	Retrosternal chest pain Pain onset with exertion or emotional stress Pain relieved by rest or nitroglycerin Pain radiation to jaw, neck, shoulders, arm, back, epigastrium Associated symptoms of dyspnea, nausea, vomiting, lightheadedness, diaphoresis
Atypical Angina Pectoris (AAP)	Only 2 of the 3 characteristics of TAP (especially in women and diabetics) Pain: pleuritic, burning, aching, soreness, reproducible Other symptoms excluding chest pain: Unusual fatigue Unusual shortness of breath Upper back pain Epigastric pain Flu-like symptoms Dizziness Generalized anxiety Generalized weakness Indigestion Palpitations
Pseudo Angina Pectoris (PAP) (aka, non-cardiac chest pain)	Only 1 of the 2 characteristics Pain is of non-cardiac origin (i.e., psychic, cranial, neck, thoracic, abdominal, pelvic, lower extremity)

Best Coronary Angiographic Views

The right anterior oblique (RAO) caudal view was best for reviewing the left circumflex artery (LCX) (Figure 1), and the left anterior oblique (LAO) caudal view was used for the right coronary artery (RCA) (Figure 2). The left anterior descending artery (LAD) was seen best with the anterior-posterior (AP) cranial view. (Figure 3) These views were selected because they could show all movements of the blood flow at the full length of the index artery on a clean background of the lungs. The selected angles avoided superposing the arteriograms or venograms on the bony structures of the spine or the myocardium filled with contrast at the end of the arterial phase and during the venous phase.

Review of Coronary Angiogram

Each coronary angiogram was reviewed by two junior angiographers. A senior interventional cardiologist reviewed the data and decided when there was disagreement between the junior angiographers. The reviewers accessed the EPIC Electronic Health Record System data, downloaded the complete CAG, and selected the series needed. Then, with the cine-angiogram running, the reviewers made a “right click” on the computer mouse, selected the Key Image option, and used the Up and Down arrow keys to move the images, one at a time, at desired speed. The time was calculated as the interval between images equal to 0.06 seconds or

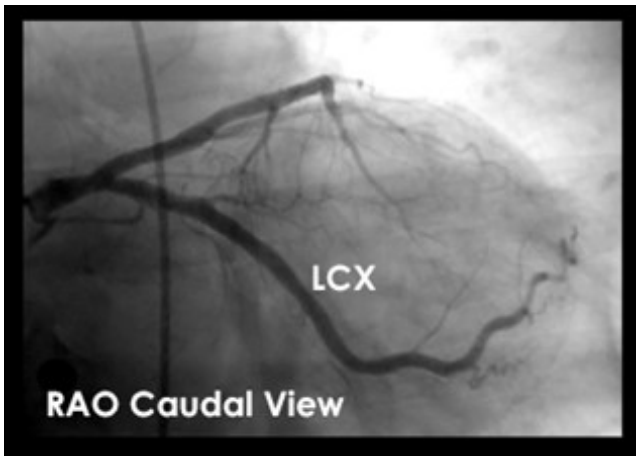

FIGURE 1. The left circumflex artery at the right anterior oblique caudal view.

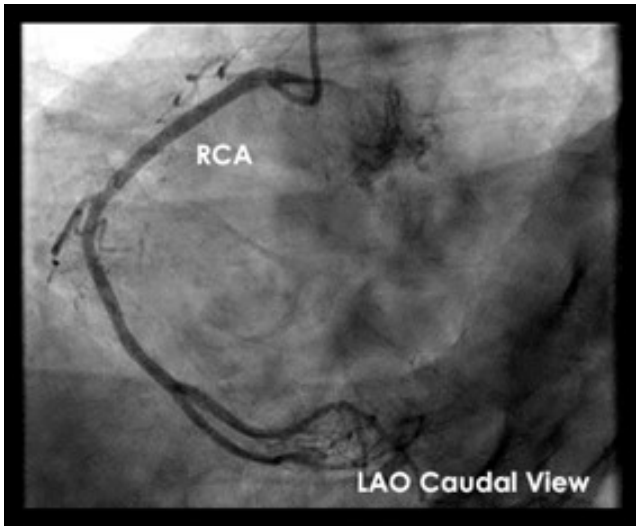

FIGURE 2. The right coronary artery at the left anterior oblique caudal view.

67 milliseconds (msec) based on a speed of recording of 15 images per second. Each image of the CAG was de-identified with the demographic information removed and saved in a PowerPoint® (Microsoft Windows) file. This way, the angiogram's images could be reviewed offline without re-accessing the security and firewall-protected EPIC system.

Data Collection

The first set of measurements was the four periods of times for the blood flow (1) to arrive at the mid-segment of the RCA (mMID), (2) at the beginning of the distal segment (bDIS), (3) at the origin of the posterior distal artery (PDA), and (4) when all the contrast disappeared from the arteries. The second measurement was the arterial phase (AP) which started from the entry of the blood into the ostium of the index artery and ended when all the contrast disappeared from the distal arterial vasculature. All the study patients' arterial phases of the LAD, LCX and RCA were recorded

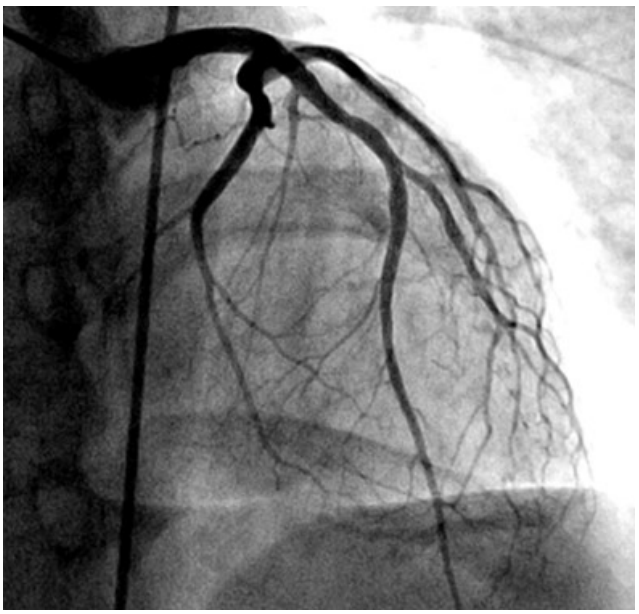

FIGURE 3. The left anterior descending (LAD) in the antero-posterior cranial view. In this view the LAD is inside a triangle with the spine in the right, the cardiac border in the left and the diaphragm at the base. The LAD is well contrasted on a clear background of the lungs.

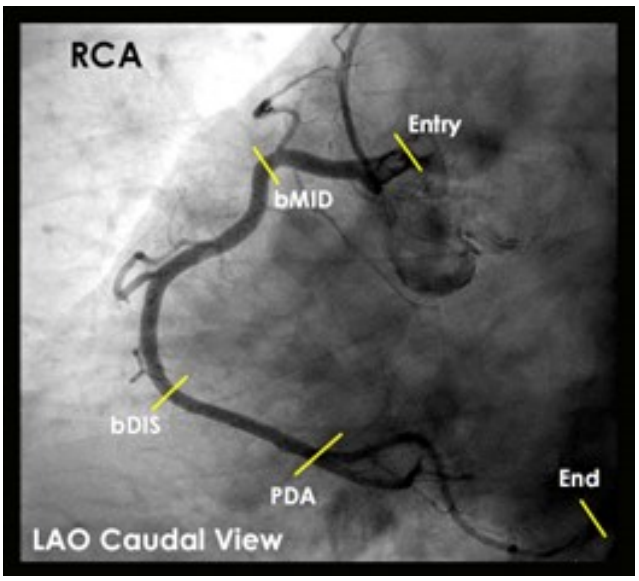

FIGURE 4. The right coronary artery and its segments. bMID (beginning of the mid-segment), bDIS (the beginning of the distal segment), PDA (Posterior descending artery)

and compared with the control. In the RCA, the last period of time to be measured started when the contrast arrived at the origin of the PDA or posterior-lateral branch (PLB), and ended when the contrast was seen filling up the main coronary sinus. This period of time reflected the transit of blood in the myocardium and was called the myocardial phase (Figure 4). The venous and myocardial phases of the LAD and LCX were not seen well in the angiogram and therefore not calculated.

TABLE 2. Demographic and Clinical Features

	Mean ± SD or N (%)
Age (years)	65 ± 7
Gender	
Male	20%
Female	80%
Cigarette smoking	30%
Commorbidity	
Diabetes mellitus	35%
Hypertension	43%
Coronary artery disease	42%
Previous heart failure	55%
Anemia	6%
Dyslipidemia	45%

Statistical Analysis

Categorical data are presented as frequency (percentage), and a comparison between groups was performed using the chi-square test or Fisher exact test. Continuous variables were presented as mean ± standard deviation (SD) for normal distribution and compared using Student's *t*-test or expressed as median (interquartile range) for non-normal distribution and compared using Wilcoxon rank-sum test. Statistical analysis was performed using the MedCalc® software program (MedCalc Software, Ltd., Belgium) for Windows (Microsoft Windows), Version 19.9.7. A *p*-value of <0.05 was considered statistically significant.

Ethical Standard

This study was conducted by the School of Medicine Research Consortium and was approved by the local ethical committee of the affiliated hospitals.

RESULTS

Subject Demographics

Sixty patients (mean age= 65±7, 80% female) met the inclusion criteria. Ten female patients with normal coronary arteries and left ventricle (LV) function served as a control group. The demographic and clinical features of the subjects are summarized in Table 2.

Duration of Arterial Phase

In the control group, the duration of the arterial phase (AP) of the RCA was 1.62 sec while it was 3.79 sec for the patients with syndrome X (p<0.05) (Figure 5).

Time Periods of Blood Flow

Four-time periods for the blood flow were measured. These were: (1) to arrive at the mid-segment of the RCA (mMID), (2) at the beginning of the distal segment (bDIS), (3) at the origin of the posterior distal artery (PDA), and (4) when all the contrast disappeared from the arteries. These data are summarized for all patient groups in Table 3 and Figure 6.

There was no difference in the first part of the AP from the time of entry to the middle of the midsegment (mMID). Both

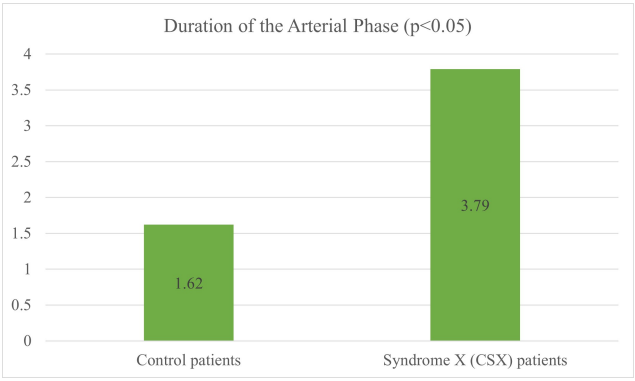

FIGURE 5. Graphical Representation the Duration of the Arterial Phase. The duration of arterial phase was 1.62 sec vs. 3.79 sec, in control vs. CSX patients, respectively.

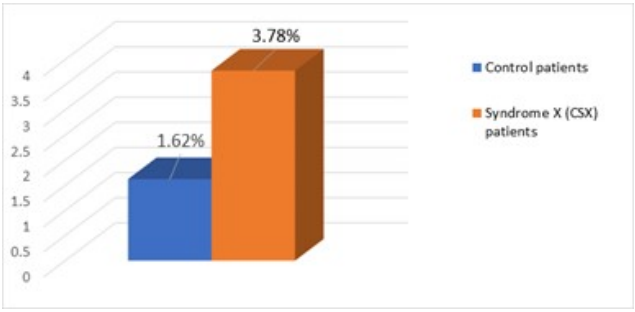

FIGURE 6. TTime Periods of Blood Flow in Control vs. CSX Groups.

were 0.5 sec (p>0.05). In the second part, from the mMID segment to the beginning of the distal segment (bDIS), the patients with CSX had a much longer delay in AP when compared with the control (0.81 vs. 0.26 sec) (p<0.05). This period of time was mainly in systole. In the third part, from the beginning of the distal segment (bDIS) to the origin of the PDA, the average duration was 0.81 sec in the patients with CSX compared with 0.41 sec in control patients. The largest difference occurred during the period of time when the contrast left the PDA until it was flushed out of the distal vasculature (1.66 sec in CSX vs. 0.45 sec in the normal control).

In the patients with long AP (3.78 sec) due to CSX, there was one group (AB) with a prolonged myocardial phase

TABLE 3. Time Periods for Blood Flow in the Right Coronary Artery.

Time (seconds)	Control	CSX				
		ABC	A	B	C	AB
Entry to mMID	0.50	0.51	0.72	0.44	0.5	0.51
mMID to bDIS	0.26	0.81	0.78	0.63	1.06	0.67
bDIS to PDA	0.41	0.81	0.48	0.78	0.98	0.71
PDA to end	0.45	1.66	1.65	1.96	1.24	1.89
Arterial Phase	1.62	3.79	3.63	3.81	3.78	3.78

(1.89 sec). These patients had dense and prolonged contrast retention at the myocardium, while in the patients of group C (same prolonged AP), the myocardial phase was shorter (1.24 sec) and had no prolonged contrast retention compared with group AB above.

If the delay was in the RCA, the patient had more SOB, palpitation, and leg edema even with normal EF. If the delay was in the LAD, the patient complained more of chest pain and fatigue.

DISCUSSION

A literature review shows no prior, published research study identifying blood flow patterns (i.e., laminar, turbulent, retrograde, and retention flow) and correlating these flow patterns to different types of lesions in the coronary artery system. The reason for this is that previous imaging technology/methods could not show the flow patterns in the arteries, frame-by-frame, with exact location, movement, and duration.

Another novel aspect of this new format allows the investigators to save the CAG image-by-image in a PowerPoint file. This format allowed for multiple repeat reviews, documentation, and tabulation of normal or abnormal features by the junior investigators and rechecked by senior investigators if needed. This method of reviewing images one by one at a slow speed allowed scrutinizing the details of flow that would not have been able to be discovered at the current reviewing speed of cine-angiography on a laptop or desktop.

The main finding of this study was that the delay of oxygenated blood flow to the myocardium was pronounced in CSX patients. The duration of the arterial phase was much longer in CSX compared to those in the control group (3.79 sec vs. 1.62, $p<0.05$), with the main delay during the myocardial phase (1.66 sec in CSX vs. 0.45 in the control group, $p<0.05$). It is reasonable to suggest that this delay resulted in suboptimal oxygen renewal at the myocardial level even when the coronary arteries were patent. The late arrival was most likely caused by excessive constriction of the microvascular network (5) during systole (or adrenergic overtone) [19], [20]. This intense vasoconstriction may delay the exit of contrast from the myocardium. This observation was supported by the present investigation results showing a prolonged retention of contrast during the myocardial phase. It can be suggested with a reasonable degree of medical certainty that the delay of new blood supply was the cause of chest pain (if in the LAD or fatigue due to lower cardiac output) and SOB or fatigue (if the culprit artery was the LCX or RCA). The reason is explained by the slow renewal of oxygen in the blood supply at the myocardial level. This raises an important question: What could be the cause? One of the significant observations was that the distal RCA, the PDA, and posterior-lateral branch (PLB) operated in a confined space, under the constant pressure of the left ventricle (when the patient was in a standing position). The movement of the blood flow in the distal RCA showed different levels of constraint compared with the free blood flow of the mid-to-distal LAD and a non-dominant LCX with a large obtuse marginal. In this situation, the RCA needs beta1 agonist stimulation to keep the artery open for blood flow. Any excessive adrenergic environment would interfere with the flow of the RCA. In contrast, the effect of adrenergic overtone would not significantly affect the function of the LAD or non-dominant LCX.

If the blood supply to the distal myocardium is delayed because of the slow exchange of blood, what options does contemporary cardiology have to offer to CSX patients? What is the role of beta-blockers in this type of functional ischemia? Does bi-ventricular pacing help? As mentioned above, beta-blockers may be effective if the patient has adrenergic overtone, which causes vasoconstriction. Further studies are needed to clarify those discussed above and intriguing questions.

Limitations

The study has different limitations. First, this is a non-randomized observational study in which the patient sample was small. Second, data were reviewed in a retrospective methodology, and third, the impact of all confounding factors such as classical risk factors, comorbidities, etc., could not be assessed. A larger cohort of patients' needs to be enrolled prospectively to confirm the above findings.

CONCLUSIONS

In the diagnosis of patients with CSX, the mechanism of pain is the prolonged arterial phase that deprives the myocardium of highly oxygenated blood, triggering ischemia. The primary delay most likely occurred at the microcirculation in the myocardium. The secondary delay happened at the epicardial level due to the slow advancement of the blood flow from the mid segment to the distal segment. The application of this new imaging technique allows for a new understanding of the mechanism of ischemia underlying CSX. Thus, it leads to developing effective strategies for preventing and managing ischemia in CSX-affected patients.

CONFLICTS OF INTEREST

None of the authors have conflicts of interest to declare

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