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QT Dispersion As A Predictor of Coronary Slow Flow in Patients with Stable Coronary Artery Disease: A Clinical Tool for An Invasively Diagnosed Entity

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ABSTRACT

Background: QT dispersion is the interval between the longest QT (QTmax) as well as the shortest QT (QTmin) recorded on a surface 12-lead electrocardiogram. It has a predictive value for ventricular arrhythmias including patients with ischemic heart diseases as well. Coronary slow flow has been always an ambiguous entity on the scale of ischemic heart disease. The predictive value of QT dispersion for coronary slow flow may add a non-invasive tool for the identification of these patients.

Objectives: Evaluation of QT dispersion in the prediction of coronary slow flow phenomena in patients having stable coronary artery disease experiencing coronary angiography.

Results: In patients having coronary slow flow, QTc dispersion is prolonged.

Conclusion: In patients having stable coronary artery disease, QTc dispersion can be employed as a simple non-invasive approach for predicting coronary slow flow; coronary slow flow is not necessarily associated with a benign course, as evidenced by the fact that these patients exhibit a prolonged QT dispersion.

Keywords: Coronary artery disease - Coronary Slow flow – ICA- QTc dispersion

INTRODUCTION

Atherosclerosis, coronary microvascular malfunction, as well as coronary vasospasm are among the mechanisms that have been linked to the development of CAD [(1)]**.** Symptoms vary with different presentations such as the typical chest, chest pain during rest, or a mixed pattern reflecting a microvascular dysfunction as an underlying mechanism in subsets of patients [(2)].

Coronary microvascular dysfunction can develop when obstructive CAD is absent or even in the existence of any other myocardial disease [(3)]**,** Patients having myocarditis, dilated cardiomyopathy, or hypertrophic cardiomyopathy may experience microvascular dysfunction due to a concomitant myocardial disease [(4)] as well as in the setting of PCI or CABG [(5)].

Microvascular angina, vasospastic angina, and coronary slow flow are subsets of coronary microvascular dysfunction. Whilst microvascular dysfunction is the main pathology, they differ in a few characteristics. Microvascular angina, previously known as "cardiac syndrome X ", has a combination of chest pain as well as normal coronary angiography. Diagnosis of microvascular angina requires the following: the presence of ischemic complaint, evidence of myocardial ischemia by ECG or an imaging modality during the ischemic episode and a demonstration of the microvascular dysfunction by a provocative test in the cath lab, and definitely, lack of obstructive (>50% stenosis) CAD [(6)]**.**

Microvascular angina has a higher incidence in females, while vasospastic angina tends to occur in young population. Another notable difference is that patients with microvascular angina usually complain of atypical not stress-induced pain following a certain circadian rhythm nocturnal. ECG ischemic changes in microvascular angina are easily missed therefore, ambulatory ECG is preferred in these patients. Patients with vasospastic angina complain of a mixed pattern of chest pain and coronary vasospasm can be induced in the Cath lab [(7)].

Coronary slow flow is diagnosed when Contrast opacification within the coronary arteries is delayed without the presence of obstructive stenosis [(8)]. It is a subset of microvascular dysfunction. Many mechanisms may be involved in coronary slow flow including; endothelial malfunction [(9)], inflammatory process [(10)]**,** and subclinical atherosclerosis. Despite outwardly normal coronary arteries, IVUS revealed substantial longitudinal atherosclerosis in these patients with subclinical atherosclerosis [(11)].

Coronary slow flow had a prevalence of 1% in research by **Beltrame *et al*.** [(12)] but a further systematic evaluation of that study suggested a prevalence of 3%**,** While 5.5% of diagnostic coronary angiograms were found to be linked to diminished blood flow in the coronary arteries by research by **Hawkins *et al*.** [(8)]

Patients having coronary slow flow may be asymptomatic and then it is only a "phenomenon" or exhibit symptoms and therefore we can call it a syndrome [(8)]**.** Clinical presentations vary from chest pain, and acute coronary syndromes up to ventricular arrhythmias and cardiac death [(13)]**,** meaning that slow coronary artery blood flow is not always associated with a positive clinical outcome.

Chest pain in patients having coronary slow flow patients may happen at rest or has a mixed pattern rather than exertional chest pain, as well as, the usual presentation with acute coronary syndromes. Coronary

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slow-flow patients are mostly males, obese with a tendency for having metabolic syndrome [8, 12].

Eltahlawi *et al.* [14] emphasized that ECG as a simple investigation can provide us with many insightful data about these patients. QT dispersion is one such example, and it has been shown to increase throughout ischemia in individuals having stable CAD. It has also been linked to the risk of ventricular arrhythmia in these patients.

The difference between the longest, as well as a 12-lead ECG with the shortest QT intervals, is used to determine QT dispersion. QT dispersion adjusted for heart rate is called the corrected QT dispersion. QT dispersion represents the total summation of electrical ventricular activity involving both depolarization and repolarization. It is considered a measurement of ventricular recovery dispersion and repolarization alterations [15].

We aim in this research to raise the clinical features of patients having coronary slow flow with emphasis on the QT dispersion in these patients so that, we can determine simple, non-invasive clinical points that predict the existence of coronary slow flow and the prognosis of such entity.

PATIENTS AND METHODS

The research was conducted between 2020 and 2021 at the Cardiology departments of Zagazig University Hospitals, Matrouh Specialized Cardiothoracic also Interventional Catheterization Centre. After thoroughly explaining the study to patients, Patients were enrolled only after receiving their written informed permission. The ethical committee of Zagazig University's faculty of medicine approved the study.
This was a case-control study.

Inclusion criteria: Patients with a suspected or established stable coronary artery disease diagnosis who are indicated for invasive coronary angiography based on the most recent ESC guidelines on chronic coronary syndrome are listed below: [16]

When non-invasive tests are inconclusive, when evaluating revascularization alternatives, noninvasive tests should show high event risk only when: (e.g.; Cardiovascular mortality exceeds 3% annually. based on Duke Treadmill Score when an exercise ECG is done, area of ischemia that is ≥10% of the LV through SPECT/PET or ≥ three of 16 segments with stress-induced hypokinesia or either akinesia by stress echocardiography ….)
Patients with certain professions due to regulatory issues (e.g.; pilots, or military personnel…), when a patient doesn't respond to medical treatment or complains of angina pain at low-intensity exercise and also an initial clinical evaluation shows a higher risk of an event, early ICA without preceding non-invasive risk stratification may be a good way to find lesions that could be revascularized.

Exclusion criteria: From these patients, we excluded: Patients with atrial fibrillation, patients who had undergone CABG (Coronary artery bypass graft) surgery, and acute coronary syndrome patients.

Clinical data: The following were applied to all patients: Request that a consent document be signed, full medical history: Complete clinical evaluation. Resting 12-lead ECG with measurement of corrected QT dispersion: Each patient will have a conventional 12-lead ECG taken while they are at rest, and the QT dispersion will be calculated as the range of QT intervals, from the longest (QT max) to the shortest (QT min) [17] To eliminate the effect of heart rate on QT dynamicity, each patient received a 12-lead ECG at the same time, and a minimum of eight useable leads was required for testing. Many formulas are postulated for the calculation of QTc, from which **Eltahlawi *et al.*** [14] recommended the Bazett formula ($QTc = QT / \sqrt{RR}$).

Conventional Transthoracic echocardiography (TTE): Using echocardiographic apparatus (Vivid S5, Vivid S6, GE Medical Systems) to perform resting transthoracic echocardiographic studies in light of the American Society of Echocardiography's (ASE) recommendationsc2019 [18]. **Routine laboratory tests:** Complete blood cell count, HbA1c, random plasma glucose, fasting plasma glucose and 2h plasma glucose levels, Kidney function tests including such serum creatinine, and Complete lipid profile.

Invasive coronary angiography: Under local anesthesia, an invasive coronary angiography was conducted through the right femoral artery (2% Lidocaine SC), which used Judkins catheters as well as using iopromide (Ultravist) as such contrast agent, conventional multi-angulated angiographic pictures were captured and stored in DICOM format on a compact disc.
The number of cine-frames obtained from the time contrast is injected until it reaches the end of the left anterior descending artery, circumflex artery, and right coronary artery, is used to determine the TIMI frame count, which was used to evaluate coronary blood flow. When the dye first entered the mustache segment, the distal bifurcation segment, and the first branch of the posterolateral artery, those were the final frames for the LAD, CX, and RCA [19].
By ICA, the existence of coronary slow flow in a patient can be determined either using TIMI flow grade or TIMI frame count [20]. A TIMI-2 flow represents coronary sluggish flow and is assessed when the contrast takes three beats or more to opacify the distal segment. The TIMI flow grades range from 0 (no flow) to 3 (normal coronary flow), according to the TIMI frame count method, established by **Gibson *et al.*** [19] the minimum number of cine frames for distal vascular opacification is 21±3. Using the TIMI frame count, some studies suggest a diagnosis of coronary slow if the frame count is above the aforementioned

threshold while others suggest a count more than 2 standard deviations above the threshold [8].
Beltrame suggested criteria for the diagnosis of primary coronary slow flow, after exclusion of secondary etiologies of coronary slow flow including; no-reflow phenomenon, exogenous vasoconstrictor drug intake, ectatic vessel or presence of coronary emboli or microbubbles injection during angiography, plus the angiographic definition of coronary slow flow is simply, a corrected TIMI frame count more than 27 frames when the image is recorded at 30 frames per second, or a TIMI-2 flow demonstrating a delay in distal vessel opacification, with the absence of coronary stenosis (no lesion ≥40%) and this criteria must be found in 1 epicardial vessel at least [20].

Ethical Approval: The study was approved by the Ethics Board of Zagazig University and the patients were given all the information they need about the trial. Informed written consent was taken from each participant in the study. This work has been carried out following The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

Statistical analysis

The IBM SPSS software program, version 20.0 (Armonk, NY: IBM Corp.), was used to import the data and analyze it. Numbers and percentages were utilized to express qualitative data. The Kolmogorov-Smirnov test was used to determine the distribution's normality. Quantitative data, including mean, standard deviation, median, and interquartile range (IQR), were all described in terms of range (minimum and maximum). The significance of each piece of data was assessed at the 5% level.

RESULTS

The research comprised 162 patients who had stable coronary artery disease but were also eligible for invasive coronary angiography. After applying the criteria proposed by Beltrame for the diagnosis of coronary slow flow, patients were separated into 2 groups; Patients with coronary slow flow phenomena were included in the first group (case group) while patients having normal coronary angiography were included in the second group (control group). When ICA was conducted, the corrected TIMI frame count was computed for each patient. Patients were diagnosed with the coronary slow flow if their TFC or mTFC was more than 27 frames, or more than 2 standard deviations, from the typical reported range in any of the 3 coronary arteries. **(26)** The coronary slow flow group had the TIMI frame count values consistent with the aforementioned criteria for coronary slow flow. **(Table 1)**

Table (1): Comparison between the two studied groups according to corrected TIMI frame count.

TIMI	Slow flow (n = 81)	Control (n = 81)	t	p
LAD				
Min. – Max.	47.0 – 56.0	34.0 – 38.0	44.670*	<0.001*
Mean ± SD.	51.56 ± 3.08	35.16 ± 1.20		
Median (IQR)	51.0 (49.0 – 55.0)	35.0 (34.0 – 36.0)		
LCX				
Min. – Max.	32.50 – 40.50	2.90 – 23.10	48.152*	<0.001*
Mean ± SD.	36.34 ± 2.35	19.40 ± 2.12		
Median (IQR)	36.40 (34.40 – 38.20)	19.30 (18.70 – 20.20)		
RCA				
Min. – Max.	30.10 – 35.50	2.60 – 22.90	46.819*	<0.001*
Mean ± SD.	33.43 ± 1.47	19.41 ± 2.26		
Median (IQR)	33.80 (32.20 – 34.80)	19.30 (18.70 – 20.10)		

Each patient had a 12-lead ECG taken and the QTc dispersion was calculated. The QTc dispersion in patients having coronary slow flow was found to be longer than in the control group. (44.0 (39.0 – 49.0) versus 32.0 (30.0 – 34.0) respectively, p <0.001) as presented in **Table 2**. These results show that patients with a coronary sluggish flow are susceptible to both ventricular arrhythmias and sudden cardiac mortality. By examining the relationship between coronary slow flow and QTc dispersion, the predictive usefulness of QTc dispersion for coronary slow flow in patients having coronary angiography was assessed. QTc dispersion was found to be a sensitive, specific non-invasive parameter in predicting coronary slow flow among patients experiencing coronary angiography. QTc dispersion with a cut-off value > 36 ms was found to be 91.36% sensitive and 90.12% specific in the prediction of coronary slow-flow patients. **(Table 3 & Figure 1)**

Table (2): Comparison of the QT dispersion for the two examined groups

QT dispersion (ms)	Slow flow (n = 81)	Control (n = 81)	t	p
Min. – Max.	34.0 – 52.0	22.0 – 44.0	15.744*	<0.001*
Mean ± SD.	43.60 ± 5.19	32.49 ± 3.66		
Median (IQR)	44.0 (39.0 – 49.0)	32.0 (30.0 – 34.0)		

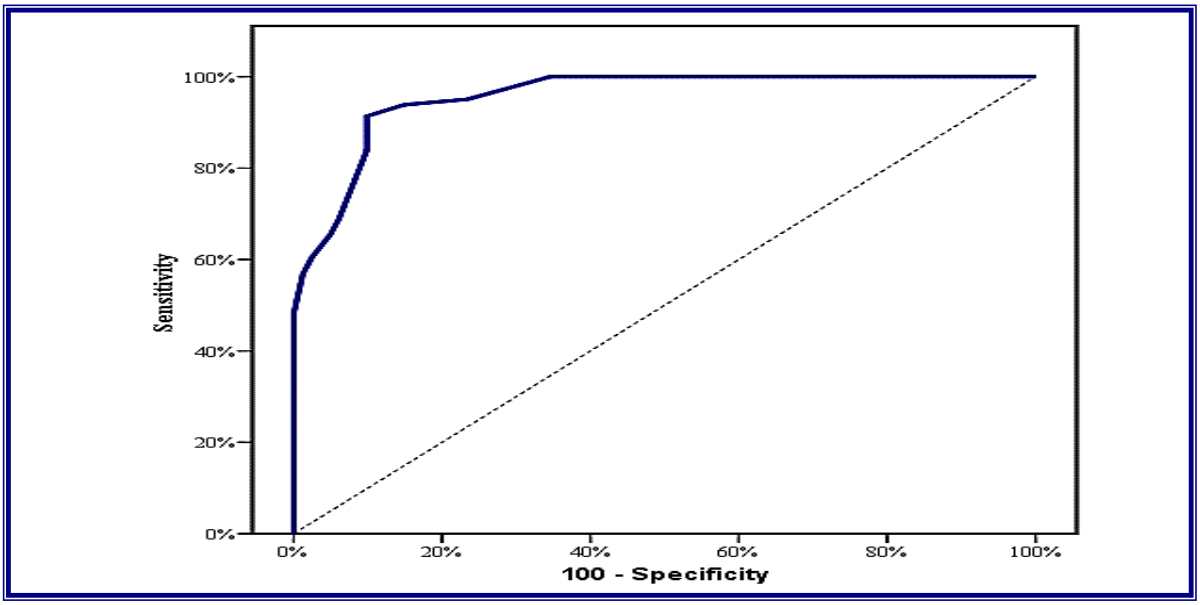

Figure (1): ROC curve for QT dispersion (ms) to discriminate Slow flow (n = 81) from control (n = 81)

Table (3): Validity (AUC, sensitivity, specificity) for QTc dispersion (ms) to discriminate Slow flow (n = 81) from control (n = 81)

	AUC	p	95% C.I	Cut off	Sensitivity	Specificity	PPV	NPV
QTc dispersion (ms)	0.956	<0.001*	0.929 – 0.983	>36	91.36	90.12	90.2	91.2

Male patients constituted most of the study population. Considering that coronary artery disease is more common in males, the male gender represented 71.6% of the slow flow group as well as 72.8% of the control group. The mean age of coronary slow flow patients and control group patients was 55.90 ± 13.22 and 58.14 ± 6.54 respectively. **(Table 4).**

Table (4): Comparison of the two examined groups based on demographic data

	Slow flow (n = 81)		Control (n = 81)		Test of Sig.	p
	No.	%	No.	%		
Sex						
Male	58	71.6	59	72.8	χ^2= 0.031	0.861
Female	23	28.4	22	27.2		
Age (years)						
Min. – Max.	33.0 – 79.0		44.0 – 77.0		t= 1.364	0.175
Mean ± SD.	55.90 ± 13.22		58.14 ± 6.54			
Median (IQR)	56.0 (44.0 – 68.0)		58.0 (54.0 – 61.0)			

Ischemic heart disease risk factors are present to various degrees in both categories, but in those with coronary slow flow, the prevalence is substantially higher. Preexisting diseases like hypertension, diabetes, dyslipidemia, and smoking are more common in the slow-flow group of patients. **(Table 5).**

Table (5): Comparison of the two examined groups concerning risk factors

	Slow flow (n = 81)		Control (n = 81)		χ^2	p
	No.	%	No.	%		
Smoking	57	70.4	21	25.9	32.044*	<0.001*
Hypertension	79	97.5	28	34.6	71.599*	<0.001*
Diabetes	57	70.4	26	32.1	23.743*	<0.001*
Dyslipidemia	68	84.0	42	51.9	19.145*	<0.001*

More than half of patients having coronary slow flow had a prior MI as well as heart failure, conversely, among the control group, the number of patients with a history of MI or heart failure was lower than the third. **(Table 6)**.

Table (6): Comparison of the two examined groups based on various parameters

	Slow flow (n = 81)		Control (n = 81)		χ^2	p
	No.	%	No.	%		
History of stroke	2	2.5	0	0.0	2.025	FEp=0.497
History of MI	66	81.5	25	30.9	42.149*	<0.001*
CHF	47	58.0	4	4.9	52.913*	<0.001*

DISCUSSION

Despite the clear angiographic definition, coronary slow flow is hard to be recognized clinically because of its atypical presentations and lack of full understanding of its pathophysiology [(21)]. Coronary slow flow is not as simple as its definition. Its clinical determinants are still indefinite, and its prognosis is not always benign. Our study's objective is to examine the correlation between coronary slow flow and QTc dispersion in terms of patient demographics and clinical features.

We studied the clinical features of patients having coronary slow flow. Coronary artery disease risk factors were found to be present in almost all of these patients. Most coronary slow-flow patients are males around the age of 50, smokers, hypertensive, and diabetics. Most of these individuals had experienced a MI before.

Investigations included 12-lead ECG with the calculation of QTc dispersion for each patient. Coronary slow flow can have a worse prognosis than it was thought before, [(22)] and QT dispersion can give insight into arrhythmic cardiac events [(15)].

QTc dispersion was observed to be considerably longer in patients with coronary slow flow (44.0 (39.0 – 49.0), p <0.001). These findings demonstrate that coronary slow flow is not necessarily a benign disease, and it can show a prognosis for ventricular arrhythmias as well as sudden cardiac death. Furthermore, QTc dispersion was evaluated for its potential in predicting coronary slow flow. With a cut-off value > 36 ms, QTc dispersion has a sensitivity of 91.36% and a specificity of 90.12% for predicting patients with the coronary sluggish flow. In conclusion, a simple non-invasive parameter like QTc dispersion can significantly predict the existence of coronary slow flow itself in a patient, as well as its prognosis.

A cohort study by **Zhu *et al.*** [(23)] demonstrated that coronary slow-flow patients are usually middle-aged particularly > 50 years old with hypertension, diabetes, and dyslipidemia. Our study's findings on the patients' features corroborate these findings.

Sanati *et al.* [(24)] agreed with our results about the patient's characteristics with affirmation that hypertension is the strongest predictor of all other risk factors.

Beltrame *et al.* [(12)] concluded that coronary slow flow is more prevalent in men. Beltrame also, in agreement with a study by **Hawkins *et al.*** [(8)] concluded that patients having coronary slow flow tend to have metabolic syndrome and to be current smokers as well.

Xia *et al.* [(25)] concluded that coronary slow flow may be equally prevalent between males and females and a study by **Huang *et al.*** [(26)] concluded that there is no substantial difference in age, smoking, hypertension, DM as well as blood pressure measurements between patients having coronary slow flow and control patients.

Regarding the QT-dispersion in coronary slow flow patients, a case-control study by **Eshraghi *et al.*** [(27)] concluded that QT-interval dispersion was significantly higher among patients having coronary slow a study by **Atak *et al.*** [(28)] demonstrated the same conclusion.

In addition to that, a 59-year-old man with coronary slow flow and recurrent syncope is described in a case report. Recurrent episodes of non-sustained ventricular tachycardia and elevated QTc dispersion (80 milliseconds) were seen on the patient's Holter ECG. This case provides further evidence linking coronary slow flow, prolonged QTc dispersion, as well

as sudden cardiac death caused by potentially fatal ventricular arrhythmias [29].

CONCLUSION

Patients with stable coronary artery disease who are candidates for invasive coronary angiography can use QTc dispersion as a non-invasive, simple approach for predicting coronary slow-flow patients.

RECOMMENDATIONS

Due to its prognostic and predictive qualities, QT dispersion should be frequently used in clinical practice for patients with stable coronary artery disease. More investigation is needed, particularly, into a coronary sluggish flow and coronary microvascular dysfunction.

DECLARATIONS

- **Consent for publication:** I attest that all authors have agreed to submit the work.
- **Availability of data and material:** Available
- **Competing interests:** None
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- **Conflicts of interest:** no conflicts of interest.

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