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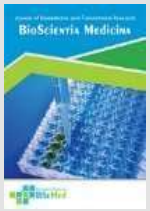

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Novel Insights into the Pathophysiology of Coronary Slow Flow Phenomenon: The Role of Triglycerides-Glucose Index and Electrocardiogram Risk Score in Subclinical Atherosclerosis

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A B S T R A C T

Background: Coronary slow flow phenomenon (CSFP) is characterized by delayed distal coronary vessel opacification without significant epicardial coronary stenosis. The underlying mechanisms of CSFP remain unclear, but subclinical atherosclerosis is a likely contributor. This study investigated the relationship between the Triglycerides-Glucose Index (TyG), Electrocardiogram Risk Score (ERS), and carotid intima-media thickness (CIMT) in CSFP patients. **Methods:** This cross-sectional study involved 31 patients diagnosed with CSFP at Dr. Mohammad Hoesin General Hospital Palembang. CSFP was determined based on coronary blood flow slowdown on angiography. Data collection included anamnesis, physical examination, laboratory tests, echocardiography, and CIMT measurement. Statistical analysis was performed using SPSS 27. **Results:** The majority of CSFP patients were male (51.6%) with a mean age of 50.87 ± 13.94 years. Dyslipidemia was the most prevalent risk factor (77.4%), followed by hypertension (35.5%), smoking (22.6%), and diabetes mellitus (6.5%). Statistical analysis revealed significant positive correlations between TyG index and CIMT ($r = 0.445$, $p = 0.012$), and between ERS and CIMT ($r = 0.476$, $p = 0.007$). **Conclusion:** TyG and ERS indices are positively correlated with CIMT in CSFP patients. These indices may be useful tools for cardiovascular risk evaluation and early identification of high-risk patients for subclinical atherosclerosis and potential CSFP.

1. Introduction

Cardiovascular diseases (CVDs) remain a leading cause of global mortality, underscoring the critical need for robust preventative strategies and early detection. Among the spectrum of CVDs, coronary slow flow phenomenon (CSFP) is an emerging area of significant interest, characterized by the delayed opacification of distal coronary vessels during angiography, in the absence of substantial stenosis in the epicardial coronary arteries. This phenomenon, while seemingly benign in its presentation, has been increasingly linked to adverse cardiovascular events, including angina, myocardial infarction, and even sudden cardiac death. The pathophysiology of CSFP remains a complex and multifaceted enigma, with various mechanisms implicated in its development. Endothelial dysfunction, a hallmark of early atherosclerotic processes, is thought to play a pivotal

role. The endothelium, the inner lining of blood vessels, is crucial in maintaining vascular homeostasis, regulating vascular tone, and preventing thrombosis. In CSFP, endothelial dysfunction disrupts these delicate processes, leading to impaired vasodilation, increased oxidative stress, and a pro-inflammatory state, all of which contribute to the observed slow coronary flow. Microvascular dysfunction, another key player in CSFP pathogenesis, further compounds the impairment of coronary blood flow. The coronary microvasculature, comprising small arteries and capillaries embedded within the heart muscle, is responsible for the fine-tuning of blood flow in response to myocardial demand. In CSFP, microvascular dysfunction manifests as impaired vasodilatory capacity, increased microvascular resistance, and diminished capillary density. These microvascular abnormalities, often in concert with endothelial dysfunction, contribute to the compromised coronary flow dynamics observed in CSFP.[1-4]

Subclinical atherosclerosis, the insidious precursor to overt CVD, is also increasingly recognized as a significant contributor to CSFP. This early stage of atherosclerosis, often asymptomatic, is characterized by the gradual buildup of lipids, inflammatory cells, and fibrous tissue within the arterial wall. This process, if left unchecked, can lead to arterial thickening and stiffening, eventually culminating in plaque formation, luminal narrowing, and increased risk of cardiovascular events. In CSFP, subclinical atherosclerosis is thought to contribute to both endothelial and microvascular dysfunction, further compromising coronary flow and setting the stage for potential adverse cardiac events. Carotid intima-media thickness (CIMT), a non-invasive marker of subclinical atherosclerosis, has emerged as a valuable tool in cardiovascular risk assessment. CIMT, measured using B-mode ultrasonography, reflects the thickness of the carotid artery wall, providing an indirect measure of systemic atherosclerotic burden. Increased CIMT has been robustly associated with an elevated risk of future cardiovascular events, including myocardial infarction and stroke. In the context of CSFP, CIMT serves as a surrogate marker for the presence and extent of subclinical atherosclerosis, aiding in risk stratification and guiding potential therapeutic interventions.[5-7]

Recent research has focused on identifying novel markers that may provide further insights into the pathophysiology of CSFP and aid in early risk stratification. The Triglycerides-Glucose (TyG) index, a simple and cost-effective indicator of insulin resistance, has shown promise in this regard. Insulin resistance, a key metabolic derangement, is increasingly recognized as a central player in the pathogenesis of atherosclerosis. It disrupts metabolic homeostasis, promotes inflammation, and contributes to endothelial dysfunction, all of which can contribute to the development of CSFP. The TyG index, calculated using fasting triglyceride and glucose levels, has been shown to correlate with increased risk of CVD and subclinical atherosclerosis, suggesting its potential utility in CSFP risk assessment. Electrocardiographic (ECG) markers have also garnered attention in the quest to identify individuals at risk for CSFP and subclinical atherosclerosis. While individual ECG abnormalities may not be sufficient to predict coronary artery disease, integrated ECG scoring systems, such as the Electrocardiogram Risk Score (ERS), have shown promise in identifying individuals at high risk for subclinical atherosclerosis. The ERS incorporates multiple ECG parameters, including heart rate, QRS duration, left ventricular hypertrophy, T-wave inversion, and QTc prolongation, to provide a comprehensive assessment of cardiac electrical activity and potential risk. These ECG markers, reflecting underlying cardiac electrical disturbances, may serve as early indicators of subclinical atherosclerosis and potential CSFP, aiding in risk stratification and guiding further investigations.[8-10] This study aimed to investigate the relationship between TyG index, ERS, and CIMT in patients with CSFP.

2. Methods

This research was designed as a cross-sectional study, a type of observational study that analyzes data from a population, or a representative subset, at a specific point in time. This design is particularly suitable for investigating the prevalence of a condition or the association between variables within a defined population. In this instance, our cross-sectional approach aimed to capture a snapshot of the relationship between the triglycerides-glucose index (TyG), electrocardiogram risk score (ERS), and carotid intima-media thickness (CIMT) in patients diagnosed with CSFP.

The study was conducted at Dr. Mohammad Hoesin General Hospital Palembang, a tertiary referral hospital in Palembang, Indonesia. The hospital serves a diverse population, providing a representative sample of patients with cardiovascular diseases. The study period spanned from January 2024 to June 2024, allowing for the recruitment of a substantial number of eligible patients. The study population consisted of 31 patients diagnosed with CSFP. The inclusion criteria were stringent to ensure the homogeneity of the study sample and the reliability of the findings. Patients were included if they had undergone coronary angiography, the gold standard for diagnosing CSFP, and had a confirmed diagnosis of CSFP based on the assessment of contrast clearance time in the coronary arteries. CSFP is characterized by delayed opacification of the distal coronary vessels, indicating slow flow, and is typically diagnosed when the contrast clearance time exceeds 3 seconds or 45 frames, given that the imaging machine captures 15 frames per second. Exclusion criteria were applied to minimize the potential confounding effects of other medical conditions that could influence the study variables. Patients with significant epicardial coronary stenosis, defined as a luminal diameter narrowing of 50% or more, were excluded to ensure that the observed slow coronary flow was not attributable to obstructive coronary artery disease. Additionally, patients with a history of acute coronary syndrome, heart failure, valvular heart disease, or chronic kidney disease were excluded to minimize the potential influence of these conditions on the study variables.

A comprehensive data collection protocol was implemented to gather relevant information on each participant. This multifaceted approach included anamnesis, physical examination, laboratory tests, echocardiography, and CIMT measurement; Anamnesis: A detailed medical history was obtained from each patient through a structured interview. This included demographic information such as age, gender, education level, and occupation, providing a socio-demographic profile of the study population. Additionally, information on medical history, specifically focusing on cardiovascular risk factors such as hypertension, diabetes mellitus type 2, and dyslipidemia was collected. Lifestyle factors, particularly smoking habits, were also documented; Physical Examination: A thorough physical examination was performed on each participant, including anthropometric measurements. Height and weight were recorded to calculate body mass index (BMI), a widely used measure of body fat. BMI was further categorized into underweight, normoweight, overweight, and obese categories based on standard classifications; Laboratory Tests: Fasting blood samples were collected from each participant to assess metabolic parameters. Triglyceride and fasting blood glucose levels were measured using standard laboratory techniques. These values were then used to calculate the TyG index, a surrogate marker of insulin resistance. The TyG index was calculated using the following formula Ln[Triglycerides (mg/dL) x Fasting blood glucose (mg/dL) / 2]; Echocardiography: Echocardiography, a non-invasive imaging technique using ultrasound, was performed to evaluate cardiac structure and function. This comprehensive assessment included measurements of left ventricular ejection fraction (LVEF), an indicator of the heart's pumping capacity, and left ventricular mass index (LVMI), a measure of the size of the heart's main pumping chamber. Diastolic function, the heart's ability to relax and fill with blood, was also assessed;

CIMT Measurement: CIMT was measured using B-mode ultrasonography, a non-invasive imaging technique that provides detailed images of the carotid arteries. This measurement reflects the thickness of the inner two layers of the carotid artery wall, the intima, and media, and serves as a surrogate marker of subclinical atherosclerosis.

The ERS was calculated based on a composite of ECG parameters, each reflecting different aspects of cardiac electrical activity. The following parameters were considered; Heart rate > 80 beats per minute; QRS duration > 110 ms; Left ventricular hypertrophy (LVH); T-wave inversion; QTc prolongation. Each parameter was assigned a score of 1 if present, resulting in a total ERS ranging from 0 to 5, with higher scores indicating a greater potential risk for subclinical atherosclerosis.

The collected data were analyzed using SPSS 27, a comprehensive statistical software package. Descriptive statistics were used to summarize the data, providing measures of central tendency, such as mean and median, and measures of dispersion, such as standard deviation and range. The Shapiro-Wilk test, a statistical test for normality, was used to assess the distribution of the data. This step is crucial in determining the appropriate statistical tests for further analysis, as many statistical tests rely on the assumption of normality. Pearson's correlation coefficient, a measure of the linear correlation between two variables, was used to analyze the correlation between TyG index and CIMT. For the analysis of the correlation between ERS and CIMT, Spearman's rank correlation coefficient, a non-parametric measure of rank correlation, was used. The choice of correlation coefficient depended on the distribution of the data, with Pearson's correlation used for normally distributed data and Spearman's rank correlation for non-normally distributed data. A p-value of less than 0.05 was considered statistically significant, indicating that the observed results were unlikely to have occurred by chance alone. This threshold is widely used in research to determine the statistical significance of findings.

3. Results

Table 1 presents the baseline characteristics of the 31 patients diagnosed with coronary slow flow phenomenon (CSFP) who participated in the study. The majority of participants were male (51.6%). This is consistent with the general trend of higher prevalence of cardiovascular diseases in men compared to women. The average age of the participants was 50.87 years, with a standard deviation of 13.94. This indicates that the study population included a range of ages, with some variability. Almost half the participants (48.4%) had completed high school, followed by those with a bachelor's degree (32.3%). A smaller proportion had only elementary (12.9%) or middle school (6.5%) education. This suggests a relatively good level of education among the participants. The participants were almost equally distributed among those working in the private sector (32.3%), government employees/military/police (35.5%), and unemployed individuals (32.3%). This distribution reflects the diverse occupational backgrounds of the study population. Nearly a quarter of the participants (22.6%) had a history of smoking, a well-established risk factor for cardiovascular disease. A small proportion of participants (6.5%) had diabetes mellitus type 2, a metabolic disorder that increases the risk of cardiovascular disease. Over a third of the participants (35.5%) had a history of hypertension, another significant risk factor for cardiovascular disease. A large majority of the participants (77.4%) had dyslipidemia, characterized by abnormal blood lipid levels, which is a major contributor to atherosclerosis and cardiovascular disease. The average body mass index (BMI) was 25.58 kg/m^2, with a standard deviation of 0.78. This places the average participant in the overweight category. Nearly half the participants (48.4%) were in the normoweight category, while 32.3% were overweight and 19.4% were obese. This indicates that a significant proportion of participants had a BMI that could contribute to cardiovascular risk.

Table 1. Baseline characteristics.

Characteristic	Mean ± SD or n (%)
Gender (male)	16 (51.6)
Age, years	50.87 ± 13.94
Education level	
Elementary school	4 (12.9)
Middle school	2 (6.5)
High school	15 (48.4)
Bachelor's degree	10 (32.3)
Occupation	
Private sector	10 (32.3)
Government employee/military/police	11 (35.5)
Unemployed	10 (32.3)
Smoking history	7 (22.6)
Diabetes mellitus type 2	2 (6.5)
Hypertension history	11 (35.5)
Dyslipidemia	24 (77.4)
Body mass index, kg/m²	25.58 ± 0.78
Body mass index categories	
Underweight (< 18.5 kg/m²)	0 (0)
Normoweight (18.5-24.9 kg/m²)	15 (48.4)
Overweight (25-29.9 kg/m²)	10 (32.3)
Obese (≥ 30 kg/m²)	6 (19.4)

Table 2 provides a summary of the laboratory findings from the 31 CSFP patients participating in the study. The mean TyG index was 8.28 ± 0.47. This index, calculated using fasting triglyceride and glucose levels, is a surrogate marker of insulin resistance. While there isn't a universally established "normal" range for TyG index, higher values generally indicate greater insulin resistance. Further analysis within the study will explore how this relates to CIMT and potential cardiovascular risk in this specific population. The mean total cholesterol level was 177.26 ± 36.76 mg/dL. This value falls within the desirable range (<200 mg/dL) according to many guidelines. However, it's important to consider this in conjunction with other lipid parameters. The mean LDL cholesterol ("bad" cholesterol) was 128.16 ± 35.07 mg/dL. This level is considered elevated and could contribute to atherosclerosis. High LDL cholesterol promotes the buildup of plaque in the arteries, increasing the risk of cardiovascular events. The median HDL cholesterol ("good" cholesterol) was 40 mg/dL (range: 29-80 mg/dL). HDL cholesterol helps remove cholesterol from the arteries, offering some protection against cardiovascular disease. While the median value is within the desirable range (>40 mg/dL for men, >50 mg/dL for women), the range indicates some individuals had low HDL, which could be a concern. The median triglyceride level was 96 mg/dL (range: 40-289 mg/dL). This is within the normal range (<150 mg/dL). However, it's crucial to remember that even within the normal range, higher triglyceride levels can still contribute to cardiovascular risk, especially when combined with other risk factors. The median fasting blood glucose was 87 mg/dL (range: 54-192 mg/dL). This falls within the normal range (<100 mg/dL), suggesting that the majority of participants did not have overt diabetes. However, the range indicates some individuals had elevated fasting glucose, which could indicate impaired glucose metabolism or prediabetes.

Table 2. Laboratory findings.

Characteristic	Mean ± SD or Median (Min-Max)
Triglycerides-glucose index (TyG)	8.28 ± 0.47
Total cholesterol, mg/dL	177.26 ± 36.76
Low-density lipoprotein (LDL) cholesterol, mg/dL	128.16 ± 35.07
High-density lipoprotein (HDL) cholesterol, mg/dL	40 (29-80)
Triglycerides, mg/dL	96 (40-289)
Fasting blood glucose, mg/dL	87 (54-192)

Table 3 presents the echocardiographic findings of the 31 CSFP patients, providing insights into their cardiac structure and function; Left ventricular ejection fraction (LVEF): The mean LVEF was 74.81 ± 8.52%. This falls well within the normal range (55-70%), indicating that the majority of patients had preserved left ventricular systolic function, meaning their hearts were pumping blood effectively; Left ventricular mass index (LVMI): The mean LVMI was 101.47 ± 25.85 g/m². This is within the normal range, suggesting no significant left ventricular hypertrophy (enlargement) in the study population; Left ventricular mass (LVM): The median LVM was 155 g (range: 94.9-309 g). This measure also supports the finding of no significant left ventricular hypertrophy; Various left ventricular dimensions: The table provides measurements of the left ventricle's internal diameter and wall thickness in both diastole (relaxed state) and systole (contracted state). These values appear to be within normal ranges, further confirming the absence of significant structural abnormalities in the left ventricle; Left atrium to aorta ratio (LA/Ao): The mean LA/Ao ratio was 0.81 ± 0.13. This is generally considered within the normal range, suggesting no significant enlargement of the left atrium; Early to late diastolic filling ratio (E/A): The median E/A ratio was 1.30 (range: 0.60-4.30). This ratio reflects the relative filling velocities of the left ventricle during early and late diastole. While the median value is within the normal range, the wide range suggests some variability in diastolic function among the participants; Early diastolic mitral annular velocity to early diastolic mitral inflow velocity ratio (E/E'): The median E/E' ratio was 10.8 (range: 6.60-20.80). This ratio is used to estimate left ventricular filling pressures. Elevated E/E' can indicate diastolic dysfunction. While the median value is within the normal range, the range again suggests variability; Diastolic dysfunction grade: A significant proportion of patients had some degree of diastolic dysfunction: 12.9% had grade 1, 45.2% had grade 2, and 3.2% had grade 3. Diastolic dysfunction refers to the heart's impaired ability to relax and fill with blood. This finding is important as diastolic dysfunction can lead to heart failure symptoms and is associated with worse cardiovascular outcomes; Isovolumetric relaxation time (IVRT) and Isovolumetric contraction time (IVCT): These parameters reflect the time intervals between the closing and opening of heart valves during the cardiac cycle. The values reported appear to be within normal ranges; Fractional shortening (FS): The mean FS was 39.83 ± 6.45%. This is a measure of the left ventricle's contractility and falls within the normal range, further supporting normal systolic function.

Table 3. Echocardiographic findings.

Characteristic	Mean ± SD or Median (Min-Max)
Left ventricular ejection fraction (LVEF), %	74.81 ± 8.52
Left ventricular mass index (LVMI), g/m²	101.47 ± 25.85
Left ventricular mass (LVM), g	155 (94.9-309)
Interventricular septal diameter (IVSD), cm	1.05 ± 0.20
Left ventricular internal diameter in diastole (LVIDd), cm	4.42 (3.66-6.18)
Left ventricular posterior wall diameter (LVPWd), cm	1.02 ± 0.20
Interventricular septum in systole (IVSs), cm	1.51 ± 0.24
Left ventricular internal diameter in systole (LVIDs), cm	2.75 ± 0.44
Left ventricular posterior wall in systole (LVPWs), cm	1.66 ± 0.23
End-diastolic volume (EDV), ml	88.6 (56.7-193)
Left atrium to aorta ratio (LA/Ao)	0.81 ± 0.13
Early to late diastolic filling ratio (E/A)	1.30 (0.60-4.30)
Early diastolic mitral annular velocity to early diastolic mitral inflow velocity ratio (E/E')	10.8 (6.60-20.80)
Diastolic dysfunction grade 1, n (%)	4 (12.9)
Diastolic dysfunction grade 2, n (%)	14 (45.2)
Diastolic dysfunction grade 3, n (%)	1 (3.2)
Isovolumetric relaxation time (IVRT), ms	90.90 ± 17.06
Isovolumetric contraction time (IVCT), ms	88.84 ± 18.97
Fractional shortening (FS), %	39.83 ± 6.45

Table 4 presents the carotid intima-media thickness (CIMT) measurements and blood flow velocities in the carotid arteries of the 31 CSFP patients; CIMT of the right carotid artery: The mean CIMT of the right carotid artery was 0.60 ± 0.16 mm; CIMT of the left carotid artery: The mean CIMT of the left carotid artery was 0.58 ± 0.13 mm; Maximum CIMT: The mean maximum CIMT (the thickest measurement from either carotid artery) was 0.63 ± 0.16 mm. To accurately interpret these CIMT values, we need to consider age- and sex-specific reference ranges. Unfortunately, the provided data lacks this information. CIMT values below 0.8 mm are often considered normal for adults. Values above 1.0 mm may indicate an increased risk of cardiovascular events. The fact that the mean maximum CIMT in this study is 0.63 mm suggests that the majority of participants likely fall within a relatively normal range. However, without specific reference values, it's difficult to draw definitive conclusions about the overall cardiovascular risk associated with these CIMT measurements. The table also provides measurements of peak systolic velocity (PSV) and end-diastolic velocity (EDV) in both carotid arteries. These velocities reflect the speed of blood flow through the arteries. The PSV values were generally higher in the left carotid artery compared to the right. This is a common finding, as the left carotid artery often has a larger diameter and carries more blood flow. The EDV values were also slightly higher in the left carotid artery. The maximum PSV and EDV values represent the highest velocities recorded from either carotid artery. Changes in blood flow velocities can sometimes indicate the presence of stenosis (narrowing) in the arteries. However, the provided data does not indicate any significant stenosis, as the velocities are generally within normal ranges. The relationship between blood flow velocities and CIMT in this study requires further analysis. It would be interesting to see if there's a correlation between higher velocities and increased CIMT, which could suggest a link between blood flow patterns and atherosclerosis development.

Table 4. CIMT measurements.

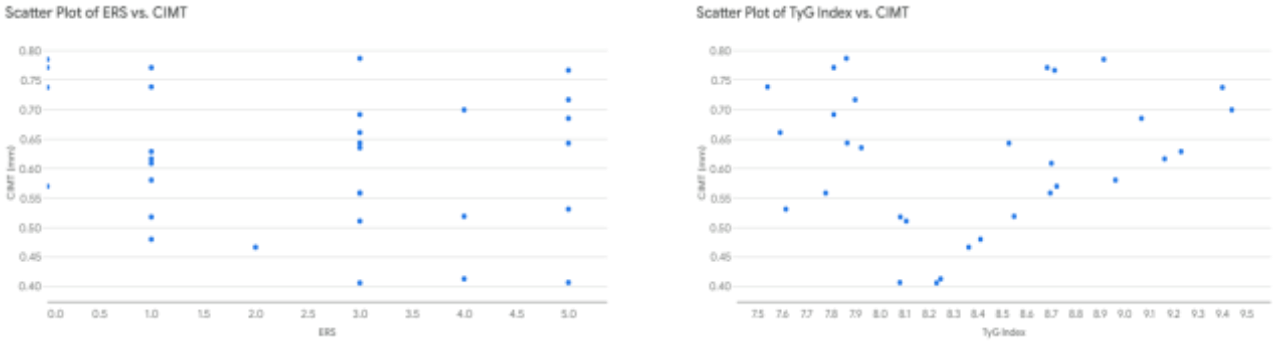
Characteristic	Mean ± SD
CIMT of the right carotid artery, mm	0.60 ± 0.16
CIMT of the left carotid artery, mm	0.58 ± 0.13
Maximum CIMT, mm	0.63 ± 0.16
Peak systolic velocity (PSV) of the right carotid artery, cm/s	83.61 ± 30.88
End-diastolic velocity (EDV) of the right carotid artery, cm/s	24.8 ± 6.64
Peak systolic velocity (PSV) of the left carotid artery, cm/s	91.51 ± 20.98
End-diastolic velocity (EDV) of the left carotid artery, cm/s	27.82 ± 8.14
Maximum PSV, cm/s	96.41 ± 28.41
Maximum EDV, cm/s	28.7 ± 8.05

Table 5 presents the results of the correlation analysis, which examines the relationship between the triglycerides-glucose (TyG) index, electrocardiogram risk score (ERS), and carotid intima-media thickness (CIMT) in the 31 CSFP patients; TyG index vs. CIMT: There was a moderate positive correlation between the TyG index and CIMT ($r = 0.445$, $p = 0.012$). This indicates that higher TyG index values were associated with greater CIMT. Since the TyG index is a marker of insulin resistance and CIMT is a marker of subclinical atherosclerosis, this finding suggests that insulin resistance may play a role in the development of atherosclerosis in CSFP patients; ERS vs. CIMT: There was also a moderate positive correlation between ERS and CIMT ($r = 0.476$, $p = 0.007$). This indicates that higher ERS scores were associated with greater CIMT. The ERS is a composite score based on ECG parameters that reflect potential cardiovascular risk. This finding suggests that ECG abnormalities, as captured by the ERS, may be indicative of underlying atherosclerosis in CSFP patients.

Table 5. Correlation analysis.

Characteristic	Correlation Coefficient (r)	p-value
TyG index vs. CIMT	445	0.012
ERS vs. CIMT	476	0.007

Figure 1 visually represents the correlations between the TyG index, ERS, and CIMT that were presented numerically in Table 5. These scatter plots provide a graphical way to see the relationships between these variables; A. ERS vs CIMT: The scatter plot clearly shows an upward trend, indicating a positive correlation. As the ERS score increases (moving right on the x-axis), the CIMT value tends to increase as well (moving up on the y-axis). This visually confirms the moderate positive correlation ($r = 0.476$) reported in Table 5. The data points are somewhat spread out, indicating some variability in the relationship. This means that while there's a general trend, not all individuals with high ERS scores necessarily have high CIMT values; B. TyG Index vs CIMT: Similar to the ERS plot, this scatter plot also shows an upward trend, confirming the positive correlation ($r = 0.445$) between the TyG index and CIMT. Higher TyG index values are generally associated with higher CIMT values. Again, there's some spread in the data points, indicating variability in the relationship. Not all individuals with high TyG index values have high CIMT.



A B

Figure 1. Scatter plot of analysis correlation. A. ERS vs CIMT. B. TyG index vs CIMT.

4. Discussion

The TyG index is a simple, cost-effective, and reliable measure of insulin resistance. It is calculated using fasting triglyceride and glucose levels, both of which are routinely measured in clinical practice. Insulin resistance is a complex metabolic disorder characterized by impaired cellular response to insulin, the hormone responsible for regulating blood sugar levels. When cells become resistant to insulin, the body compensates by producing more insulin, leading to hyperinsulinemia. This chronic state of hyperinsulinemia and elevated blood glucose levels triggers a cascade of events that promote the development of atherosclerosis, the underlying cause of many cardiovascular diseases. Insulin resistance disrupts the delicate balance of vascular health by impairing endothelial function, the ability of the endothelium (the inner lining of blood vessels) to regulate vascular tone and maintain a healthy environment. The endothelium plays a crucial role in vascular homeostasis by producing various substances that control blood vessel dilation and constriction, prevent blood clotting, and regulate inflammation. Insulin resistance disrupts these processes, leading to impaired vasodilation, increased oxidative stress (an imbalance between harmful free radicals and protective antioxidants), and a pro-inflammatory state, all of which contribute to the initiation and progression of atherosclerosis. Furthermore, insulin resistance fuels inflammation, a key driver of atherosclerosis. Chronic inflammation within the arterial wall sets the stage for the accumulation of lipids, the recruitment of immune cells, and the formation of foam cells, the hallmark of early atherosclerotic lesions. These lesions can grow and harden over time, eventually leading to plaque formation, which can obstruct blood flow and cause serious cardiovascular events. In addition to its effects on endothelial function and inflammation, insulin resistance also disrupts lipid metabolism. It can lead to increased levels of triglycerides, a type of fat found in the blood, and decreased levels of high-density lipoprotein cholesterol (HDL-C), often referred to as "good cholesterol." Both of these lipid abnormalities are associated with an increased risk of atherosclerosis. Triglycerides can contribute to the formation of atherosclerotic plaques, while HDL-C helps remove cholesterol from the arteries, offering some protection against plaque buildup. In the context of CSFP, the positive correlation between TyG index and CIMT suggests that insulin resistance may contribute to the development of subclinical atherosclerosis, which in turn may play a role in the pathophysiology of CSFP. Subclinical atherosclerosis

refers to the early stages of atherosclerosis, often occurring without any noticeable symptoms. It is characterized by the gradual buildup of plaque within the arteries, which can eventually lead to significant narrowing and obstruction of blood flow. CIMT, measured using B-mode ultrasonography, is a non-invasive marker of subclinical atherosclerosis. It reflects the thickness of the carotid artery wall, providing an indirect measure of systemic atherosclerotic burden. Increased CIMT has been robustly associated with an elevated risk of future cardiovascular events, including myocardial infarction and stroke. In the context of CSFP, CIMT serves as a surrogate marker for the presence and extent of subclinical atherosclerosis, aiding in risk stratification and guiding potential therapeutic interventions. The exact mechanisms linking subclinical atherosclerosis to CSFP are not fully understood, but several hypotheses have been proposed. Atherosclerosis may contribute to endothelial dysfunction and microvascular dysfunction, both of which are implicated in CSFP. Endothelial dysfunction impairs the production of nitric oxide, a potent vasodilator, leading to reduced coronary blood flow. Microvascular dysfunction, characterized by impaired vasodilatory capacity and increased microvascular resistance, further compromises coronary flow. The findings from this study highlight the importance of early detection and intervention in patients with CSFP, particularly those with elevated TyG index values. Insulin resistance is a modifiable risk factor, and lifestyle interventions, such as diet and exercise, can improve insulin sensitivity and potentially slow the progression of atherosclerosis. In some cases, pharmacological therapy may be necessary to manage insulin resistance and reduce cardiovascular risk.[11-13]

The electrocardiogram (ECG) has long been a cornerstone of cardiovascular assessment, providing a non-invasive glimpse into the electrical activity of the heart. While traditionally used to diagnose arrhythmias and other overt cardiac conditions, the ECG also holds valuable information about subclinical cardiovascular processes, such as atherosclerosis. The Electrocardiogram Risk Score (ERS) takes this a step further by integrating multiple ECG parameters to provide a comprehensive assessment of cardiovascular risk. The ERS incorporates a range of ECG features, including heart rate, QRS duration, left ventricular hypertrophy, T-wave inversion, and QTc prolongation. Each of these parameters can provide subtle clues about the health of the heart and blood vessels. For example, an elevated heart rate can indicate increased sympathetic nervous system activity, which has been linked to cardiovascular risk. Prolonged QRS duration may suggest underlying conduction abnormalities or myocardial damage. Left ventricular hypertrophy, an enlargement of the heart's main pumping chamber, can be a sign of increased workload on the heart, often due to high blood pressure or other cardiovascular conditions. T-wave inversion and QTc prolongation can reflect myocardial ischemia or repolarization abnormalities, which may be indicative of underlying coronary artery disease. By combining these individual ECG parameters into a composite score, the ERS provides a more comprehensive assessment of cardiovascular risk than any single ECG feature alone. This is particularly valuable in the context of subclinical atherosclerosis, where subtle ECG abnormalities may be the only early indicators of underlying disease. Subclinical atherosclerosis, the insidious precursor to overt cardiovascular disease, often lurks silently beneath the surface, without causing any noticeable symptoms. It is characterized by the gradual buildup of plaque within the arteries, a process that can begin early in life and progress over many years. This plaque buildup can eventually lead to significant narrowing and obstruction of blood flow, increasing the risk of heart attack, stroke, and other cardiovascular events. ECG abnormalities, even subtle ones, can be early harbingers of subclinical atherosclerosis. These abnormalities may reflect underlying myocardial ischemia, a condition in which the heart muscle does not receive enough oxygen to meet its needs. Myocardial ischemia can occur even in the absence of obstructive coronary artery disease, particularly in the

presence of subclinical atherosclerosis. Atherosclerosis can disrupt the delicate balance of vascular health in several ways. It can impair endothelial function, the ability of the endothelium (the inner lining of blood vessels) to regulate vascular tone and maintain a healthy environment. The endothelium plays a crucial role in vascular homeostasis by producing various substances that control blood vessel dilation and constriction, prevent blood clotting, and regulate inflammation. Atherosclerosis can also disrupt microvascular function, impairing the ability of the small blood vessels within the heart muscle to deliver oxygen and nutrients to the heart cells. This disruption of endothelial and microvascular function can lead to reduced coronary flow reserve, the ability of the coronary arteries to dilate and increase blood flow in response to increased demand. This reduced flow reserve may not be apparent at rest but can become evident during periods of increased myocardial demand, such as exercise or stress. The resulting myocardial ischemia can lead to electrical disturbances in the heart, which are reflected in the ECG as T-wave inversions, QTc prolongation, or left ventricular hypertrophy. In individuals with CSFP, the positive correlation between ERS and CIMT provides further evidence for the link between ECG abnormalities and subclinical atherosclerosis. CIMT, measured using B-mode ultrasonography, is a non-invasive marker of subclinical atherosclerosis. It reflects the thickness of the carotid artery wall, providing an indirect measure of systemic atherosclerotic burden. Increased CIMT has been robustly associated with an elevated risk of future cardiovascular events, including myocardial infarction and stroke. In the context of CSFP, CIMT serves as a surrogate marker for the presence and extent of subclinical atherosclerosis, aiding in risk stratification and guiding potential therapeutic interventions. The positive correlation between ERS and CIMT suggests that ECG abnormalities, as reflected in the ERS, may be indicative of underlying subclinical atherosclerosis in CSFP patients. This finding is consistent with previous studies that have linked individual ECG abnormalities, such as T-wave inversion, QTc prolongation, and left ventricular hypertrophy, to subclinical atherosclerosis and cardiovascular risk. The findings from this study have important clinical implications for the management of CSFP patients. The ERS could potentially be used as a non-invasive tool to identify CSFP patients at higher risk for subclinical atherosclerosis and subsequent cardiovascular events. Early identification of these individuals could allow for timely intervention and risk factor modification to potentially slow the progression of atherosclerosis and reduce the risk of complications. Lifestyle modifications, such as diet and exercise, can play a crucial role in managing cardiovascular risk factors and preventing the progression of atherosclerosis. In some cases, pharmacological therapy may be necessary to control blood pressure, lower cholesterol levels, or manage other cardiovascular risk factors. Close monitoring is also essential for CSFP patients, especially those with elevated ERS scores, to assess the progression of atherosclerosis and identify any potential complications.[14-17]

This study's findings have the potential to significantly impact the clinical management of patients with CSFP. By demonstrating the positive correlation between TyG index, ERS, and CIMT, this research highlights the potential of these markers as cost-effective screening tools to identify individuals at high risk for subclinical atherosclerosis and potential CSFP. Early intervention in these patients, encompassing lifestyle modifications, pharmacological therapy, and close monitoring, may help prevent the progression of atherosclerosis and reduce the risk of cardiovascular events. Lifestyle modifications play a crucial role in managing cardiovascular risk factors and preventing the progression of atherosclerosis. These modifications represent a cornerstone of cardiovascular health and empower patients to take an active role in their well-being. A heart-healthy diet is fundamental to managing cardiovascular risk factors. Reducing saturated and trans fats, which are

found in many processed foods and fatty meats, can help lower LDL cholesterol levels. Increasing the intake of fruits, vegetables, and whole grains provides essential nutrients, fiber, and antioxidants that support cardiovascular health. Limiting sugar intake helps regulate blood glucose levels and reduces the risk of insulin resistance. Regular physical activity is another essential component of a heart-healthy lifestyle. Exercise helps improve insulin sensitivity, making the body's cells more responsive to insulin and better able to regulate blood glucose levels. It also helps lower blood pressure, reducing the strain on the heart and blood vessels. Additionally, physical activity can promote weight loss, which further contributes to cardiovascular health. Smoking is a major risk factor for atherosclerosis and cardiovascular disease. It damages the endothelium, the inner lining of blood vessels, and promotes inflammation, both of which contribute to the development of atherosclerosis. Smoking cessation is one of the most significant lifestyle modifications a person can make to improve their cardiovascular health. While lifestyle modifications are essential, pharmacological therapy may be necessary for individuals with elevated TyG index or ERS, indicating increased cardiovascular risk. Statins are a class of cholesterol-lowering medications that are often recommended to reduce LDL cholesterol levels and prevent plaque buildup in the arteries. Statins work by inhibiting an enzyme in the liver that is responsible for producing cholesterol. By lowering LDL cholesterol levels, statins can help slow the progression of atherosclerosis and reduce the risk of cardiovascular events. Antiplatelet medications, such as aspirin, may also be prescribed to reduce the risk of blood clots. Blood clots can form in the arteries when plaque ruptures, potentially leading to heart attack or stroke. Antiplatelet medications help prevent blood clots by interfering with the function of platelets, the cells responsible for blood clotting. For individuals with hypertension, antihypertensive medications may be necessary to control blood pressure and reduce the strain on the heart and blood vessels. There are several classes of antihypertensive medications, each working through different mechanisms to lower blood pressure. The choice of medication depends on individual patient factors and any coexisting medical conditions. Close monitoring is essential for CSFP patients, especially those with elevated TyG index or ERS. Regular follow-up appointments with a healthcare provider can help assess the progression of atherosclerosis and identify any potential complications. During follow-up appointments, healthcare providers may assess cardiovascular risk factors, such as blood pressure, cholesterol levels, and blood glucose levels. They may also conduct physical examinations and order additional tests, such as ECGs or echocardiograms, to evaluate heart health. Close monitoring can help identify potential complications of atherosclerosis, such as angina (chest pain), shortness of breath, or peripheral artery disease (reduced blood flow to the limbs). Early detection of these complications allows for prompt intervention and can help prevent more serious cardiovascular events. In some cases, additional investigations, such as coronary angiography or cardiac computed tomography angiography, may be necessary to evaluate the coronary arteries in more detail. These imaging tests can provide detailed pictures of the coronary arteries, helping to identify any areas of narrowing or blockage. The findings from this study underscore the importance of early detection and intervention in patients with CSFP. By identifying individuals at high risk for subclinical atherosclerosis and potential CSFP, healthcare providers can implement strategies to manage cardiovascular risk factors and potentially slow the progression of atherosclerosis. Lifestyle modifications, pharmacological therapy, and close monitoring are all critical components of this comprehensive approach to cardiovascular care.[18-20]

5. Conclusion

In conclusion, this research has illuminated significant correlations between the TyG index, a marker of insulin resistance, and CIMT, a measure of subclinical atherosclerosis, in patients with CSFP.

Additionally, the study has underscored a positive correlation between the ERS, an indicator of ECG abnormalities, and CIMT, further emphasizing the role of subclinical atherosclerosis in CSFP. These findings hold critical implications for the clinical management of CSFP patients. The TyG index and ERS may serve as cost-effective screening tools for identifying individuals at high risk for subclinical atherosclerosis and potential CSFP. Early detection and intervention in these patients, through lifestyle modifications, pharmacological therapy, and close monitoring, could play a crucial role in preventing the progression of atherosclerosis and reducing the risk of cardiovascular events. Further research is needed to delve deeper into the pathophysiological mechanisms linking insulin resistance, ECG abnormalities, and subclinical atherosclerosis in CSFP. Exploring these intricate relationships will pave the way for developing targeted interventions to prevent the progression of CSFP and its associated cardiovascular complications. The insights gained from this study underscore the importance of a comprehensive approach to cardiovascular care, emphasizing early detection, risk factor modification, and close monitoring in patients with CSFP. By understanding and addressing the complex interplay of factors contributing to CSFP, healthcare providers can strive towards improved patient outcomes and reduced cardiovascular risk.

6. References

1. Setoyama K, Sonoda S, Naka Y, Okabe H, Inoue K, Miura T, et al. Prognostic value of right ventricular branches slow flow phenomenon after percutaneous coronary intervention for acute coronary syndrome in the right coronary artery. J Am Coll Cardiol. 2020; 75(11): 41.
2. Huang B, Sun L, Guo Y, Liu G, Xing S, Li P, et al. Acute effects of low-level Tragus stimulation on the coronary slow flow phenomenon. J Am Coll Cardiol. 2020; 75(11): 1123.
3. Ghanie A, Partan RU, Indrajaya T, Ali Z, Saleh MI, Hidayat R. The effect of angiotensin-converting enzyme gene polymorphisms in the coronary slow flow phenomenon at South Sumatra, Indonesia population. Open Access Maced J Med Sci. 2020; 8(A): 225–30.
4. Sukandi E, Tanta Y, Indrajaya T, Ghanie A, Saleh MI, Irfannuddin, et al. Electrocardiography predictive value on coronary Slow Flow Phenomenon. Bioscmed. 2022; 6(3): 1435–42.
5. Peng Y, Wei X, Wu F, Fan M, Wang K, Zhou J. Electroacupuncture for slow flow/no-reflow phenomenon in patients with acute myocardial infarction undergoing percutaneous coronary intervention: protocol for a pilot randomized controlled trial. Front Cardiovasc Med. 2024; 11: 1401269.
6. Vairaperumal T, Tsai Z-Y, Liu P-Y. Emerging predictors by non-HDL-C/HDL-C ratio and novel biomarkers for coronary slow flow phenomenon. Acta Cardiol Sin. 2024; 40(4): 367–72.
7. Kabiri M, Mashayekhi-Sardoo H, Elyasi S, Shamsara J, Dastani M, Mohammadpour AH. Adiponectin and paraoxonase-1 correlation with thrombolysis in myocardial infarction frame count with coronary slow flow phenomenon. Hormozgan Med J. 2024; 28(3): 157–66.
8. Zhang X-J, Hou A-J, Luan B, Wang C-F, Li J-J. Uric acid to albumin ratio as a novel predictor for coronary slow flow phenomenon in patients with chronic coronary syndrome and non-obstructive coronary arteries. BMC Cardiovasc Disord. 2024; 24(1): 358.
9. Zang S-W, Long J-J, Wang Y. Neutrophil percentage to albumin ratio as a predictor for coronary slow flow phenomenon in patients with myocardial ischemia with no obstructive coronary arteries. Int J Gen Med. 2024; 17: 3511–9.

10. Soltani M, Hosseinzadeh-Attar MJ, Rezaei M, Alipoor E, Vasheghani-Farahani A, Yaseri M, et al. Effect of nano-curcumin supplementation on cardiometabolic risk factors, physical and psychological quality of life, and depression in patients with coronary slow flow phenomenon: a randomized double-blind clinical trial. Trials. 2024; 25(1): 515.
11. Zhang X-J, Hou A-J, Luan B, Wang C-F, Li J-J. Uric acid to albumin ratio as a novel predictor for coronary slow flow phenomenon in patients with chronic coronary syndrome and non-obstructive coronary arteries. BMC Cardiovasc Disord. 2024; 24(1): 358.
12. Soltani M, Hosseinzadeh-Attar MJ, Rezaei M, Alipoor E, Vasheghani-Farahani A, Yaseri M, et al. Effect of nano-curcumin supplementation on cardiometabolic risk factors, physical and psychological quality of life, and depression in patients with coronary slow flow phenomenon: a randomized double-blind clinical trial. Trials. 2024; 25(1): 515.
13. Chen Y-D, Wen Z-G, Long J-J, Wang Y. Association between systemic inflammation response index and slow coronary flow phenomenon in patients with ischemia and no obstructive coronary arteries. Int J Gen Med. 2024; 17:4045–53.
14. Khalil MA, Khalfallah M, Elsheikh A. Predictors and clinical outcomes of slow flow phenomenon in diabetic patients with chronic coronary syndrome. BMC Cardiovasc Disord. 2024; 24(1): 518.
15. Khansari N, Salehi AM, Mohammadi N, Yazdi AH, Sanaei Z. Evaluation of changes in the global longitudinal strain for left ventricular function before and after eight weeks of taking high dose of atorvastatin in patients with coronary slow flow phenomenon. BMC Cardiovasc Disord. 2024; 24(1): 522.
16. Pasupathy S, Tavella R, Zeitz C, Edwards S, Worthley M, Arstall M, et al. Randomised placebo-controlled pilot trial evaluating the anti-anginal efficacy of ticagrelor in patients with angina with nonobstructive coronary arteries and coronary slow flow phenomenon. J Clin Med. 2024; 13(17): 5235.
17. Beltrame JF, Cutri N, Kopetz V, Tavella R. The role of nitric oxide in the coronary slow flow phenomenon. Coron Artery Dis. 2014; 25(3): 187–9.
18. Aksan G, Soylu K, Aksoy O, Özdemir M, Yanik A, Yuksel S, et al. The relationship between neutrophil gelatinase-associated lipocalin levels and the slow coronary flow phenomenon. Coron Artery Dis. 2014; 25(6): 505–9.
19. Kalyoncuoglu M, Biter Hİ, Ozturk S, Belen E, Can MM. Predictive accuracy of lymphocyte-to-monocyte ratio and monocyte-to-high-density-lipoprotein-cholesterol ratio in determining the slow flow/no-reflow phenomenon in patients with non-ST-elevated myocardial infarction. Coron Artery Dis. 2020; 31(6): 518–26.
20. Nakao Y, Inaba S, Kinoshita M, Sumimoto T, Saito M, Aono J, et al. Usefulness of intravascular ultrasound assessment after development of the slow flow phenomenon during percutaneous coronary intervention. Coron Artery Dis. 2022; 33(4): 302–10.