

Invited Editorial / Davetli Editöryal Yorum

Coronary slow flow

Koroner yavaş akım

Veysel Oktay, M.D., Alev Arat Özkan, M.D.

Cardiology Institute, İstanbul University, İstanbul, Turkey

Coronary slow flow is the slow antegrade passage of dye through 1 or more vessels of the coronary tree. It can result from coronary macro- or microvascular obstruction of any cause, and can be transient or persistent. Inadvertent injection of microbubbles are likely the most frequent cause of transient slow flow. The no-reflow phenomenon, a nightmare of any interventional cardiologist, is the most extreme form of coronary slow flow, and arises from distal embolization of atherosclerotic or thrombotic material and release of vasoactive substances. Slow flow can be caused by coronary stenosis as well as by coronary ectasia, due to the capacitance effect of filling the large vessel. In 1972, Tambe et al. described “coronary slow flow phenomenon” (CSFP) in 6 subjects presenting with chest pain syndromes. Distinct from Syndrome X, this group was characterized by the finding of delayed coronary opacification in the absence of obstructive epicardial disease.^[1] Since its original description, this phenomenon has been associated with other forms of ischemia, including myocardial infarction and arrhythmia, as well as increased cardiovascular mortality. Clinical features and underlying pathophysiologic mechanisms of this entity have been investigated in several studies. Increased resting resistance of the microvascular coronary arteries is thought to play a major role in pathophysiology, and due to the possible role of neuropeptide Y, the name “cardiac syndrome Y” has been suggested.^[2]

Due to discrepancies in defining CSFP, incidence ranges of 1–7% in angiographic series, and up to 5% in cases of acute coronary syndromes, have been reported.^[1,3]

There are 2 methods of quantifying “slow flow.” Thrombolysis in myocardial infarction (TIMI) flow grade scores contrast flow from TIMI 0 (no flow) to TIMI 3 (normal flow, distal vessel is opacified in less than 3 beats). TIMI 2 flow involves delayed filling. The second method is the corrected TIMI frame count, which is the number of frames required for contrast material to reach a specified distal coronary artery point with a normal range of 21 ± 3.5 .

Demographic and clinical characteristics of CSFP have been described in several patient groups, most of which are comprised of young males, the majority of whom present with acute coronary syndrome (ACS) and are smokers.^[3,4] Association with obesity, metabolic syndrome, hyperlipidemia, or renal impairment is controversial.^[5] Studies in patients with impaired renal function suggests independent association between glomerular filtration rate and CSFP.^[6,7] As chronic kidney disease is an established risk factor

Abbreviations:

ACS	Acute coronary syndrome
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CSFP	Coronary slow flow phenomenon
e-GFR	estimated glomerular filtration rate
MDRD	Modification of Diet in Renal Disease
TIMI	Thrombolysis in myocardial infarction



for cardiovascular disease, association with CSFP and early stages of renal function loss are to be expected.

In the current issue of the Archives of the Turkish Society of Cardiology, Çabuk et al. aimed to investigate the relationship between CSFP and normal to mildly impaired renal function using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation, which was developed in 2009 to overcome underestimation in patients with estimated glomerular filtration rate (e-GFR) levels ≥ 60 ml/min/1.73 m², using the Modification of Diet in Renal Disease (MDRD) equation.^[8] It has provided less bias and improved risk stratification, compared to other formulas. A total of 370 stable angina patients, 198 with CSFP and 172 with normal coronary flow with e-GFR values between 60 and 120 ml/min/1.73 m² using the CKD-EPI equation were included in the study, and in contrast to previous reports in which the MDRD equation was used, no association between CSFP and normal to mildly impaired renal function was found.^[6,9,10] Between the normal and slow coronary flow groups, no significant differences were found in e-GFR levels (calculated either by CKD-EPI or MDRD formulas). Only in the subgroup of patients with e-GFR (MDRD) ≥ 90 mL/min/1.73 m² (e-GFR [MDRD ≥ 90]), were mean e-GFR levels found to be lower in the CSFP group (107.0 \pm 12.7 vs 102.7 \pm 10.0, p=0.02). This may implicate a complex interaction between renal function and coronary flow, which may be different among patients with normal and reduced GFRs. Reduced glomerular filtration rate in the normal range may be a characteristic of CSFP, whereas in those with reduced renal function, coronary slow flow may be a secondary finding. A similar study by Akın et al., which targeted the same population but in which the MDRD formula was used, found that uric acid and e-GFR were independent correlates of CSFP in patients with normal to

mildly impaired renal function.^[9] In the study in the present issue, the CSFP group had higher smoking and sedimentation rates, red cell distribution width, mean platelet volume, and high-sensitive C-reactive protein, but lower high-density lipoprotein cholesterol levels, compared to the group with normal coronary flow. The primary limitation of the study was the same as that of others, namely, the definition of CSFP and subsequent patient selection. In each of these studies, CSFP is defined as slow flow in so-called “normal” epicardial arteries. Thus, some researchers included patients with nonsignificant (<50%) lesions, while others only included those with totally normal epicardial arteries.^[3,4] To quantify slow flow, some use TIMI flow grade, while others use TIMI frame count. As mentioned above, a reference value of 21 \pm 3 frames is used, and some investigators have used the baseline as a threshold, while others used reference ± 2 SD as a threshold for slow flow. For those using TIMI flow grade, it is noteworthy that a TIMI 2 flow corresponds to a frame count of >50. The number of vessels involved also differs between studies. While some investigators include only patients with CSFP in all 3 coronaries, others include those with only 1 vessel that meets the criteria.^[3]

Çabuk et al.^[8] included patients without obstructive disease, so that we may presume the population was heterogenous, consisting of those with smooth coronaries, as well as those with non-obstructive plaques, which surely had an impact on the results. As mentioned by the authors themselves, intravascular ultrasound (IVUS) imaging was needed to overcome this limitation, so that an accurate diagnosis of normal coronaries could be made. Another limitation was the lack of information about the heart rates of patients during angiography, which is an important parameter of microvascular function, influencing frame count.

Table 1. Beltrame criteria for diagnosing primary coronary slow flow^[11]

1. Angiographic evidence of CSFP, defined by:
 - a. No evidence of obstructive epicardial coronary artery disease (CAD) (no lesions $\geq 40\%$).
 - b. Delayed distal vessel contrast opacification as evidenced by either: TIMI 2 flow (requiring ≥ 3 beats to opacify the vessel) or corrected TIMI frame count >27 frames (images acquired at 30 frames/s).
 - c. Delayed distal opacification in at least 1 epicardial vessel.

Exclusion of secondary causes of CSFP, including no-reflow phenomenon, coronary emboli, coronary ectasia, and exogenous vasoconstrictor administration.

The authors performed a retrospective analysis, and interestingly, included only patients with stable angina and documented ischemia, excluding those with ACS. In spite of discrepancies in definition, some clinical findings common to those of previous series were reported. Rest or mixed-pattern angina is a distinguishing characteristic of CSFP, and ACS is the major indication for coronary angiography in most series. Coronary hemodynamic studies have demonstrated an increase in resting microvascular resistance with preserved flow reserve. Preserved exercise tolerance is confirmed by studies that have documented a decrease in coronary resistance and better perfusion with exercise in patients with CSFP.^[2,5] For this reason, the reported population may not fully represent all patients with SCFP, but only a subgroup.

CSFP is a multifactorial entity in which inflammatory status as well as hemodynamics plays an important role. Reported findings of most series are hampered by heterogeneity of included patients, angiographic inclusion criteria, small sample size, and retrospective nature. To understand the underlying mechanism, associated factors, and prognosis of this complex entity, further large-scale prospective studies that assess clinical, hemodynamic, and metabolic/inflammatory factors, with well-defined inclusion criteria, are needed. Recently, this phenomenon was classified as a subgroup of coronary vasomotor dysfunction, and Beltrame proposed well-defined criteria (Table 1) for diagnosing “Primary Coronary Slow Flow,” which will certainly contribute to an improvement in future studies.^[11]

Conflict-of-interest issues regarding the authorship or article: None declared.

REFERENCES

1. Tambe AA, Demany MA, Zimmerman HA, Mascarenhas E. Angina pectoris and slow flow velocity of dye in coronary arteries—a new angiographic finding. *Am Heart J* 1972;84:66–71. [CrossRef](#)
2. Fineschi M, Bravi A, Gori T. The “slow coronary flow” phenomenon: evidence of preserved coronary flow reserve despite increased resting microvascular resistances. *Int J Cardiol* 2008;127:358–61. [CrossRef](#)
3. Beltrame JF, Limaye SB, Horowitz JD. The coronary slow flow phenomenon—a new coronary microvascular disorder. *Cardiology* 2002;97:197–202. [CrossRef](#)
4. Hawkins BM, Stavarakis S, Rousan TA, Abu-Fadel M, Schechter E. Coronary slow flow—prevalence and clinical correlations. *Circ J* 2012;76:936–42. [CrossRef](#)
5. Ganz P. The coronary slow flow phenomenon. Chest pain with Normal Coronary arteries. Springer 2013;101–17.
6. Yilmaz MB, Yalta K. Coronary flow slows as renal function worsens. *Clin Cardiol* 2009;32:278–82. [CrossRef](#)
7. Sobkowicz B, Tomaszuk-Kazberuk A, Kralisz P, Malyszko J, Kalinowski M, Hryszko T, et al. Coronary blood flow in patients with end-stage renal disease assessed by thrombolysis in myocardial infarction frame count method. *Nephrol Dial Transplant* 2010;25:926–30. [CrossRef](#)
8. Çabuk AK, Çabuk G, Karamanlioğlu M, Eliz Uzel K, Bağlan Uzunget S, Aslantürk ÖF, et al. Is there a relationship between slow coronary flow and normal to mildly impaired renal function? *Turk Kardiyol Dern Ars* 2016;44:207–14.
9. Akin F, Celik O, Ayça B, Yalçın AA, Altun I, Köse N. Association of glomerular filtration rate with slow coronary flow in patients with normal to mildly impaired renal function. *Angiology* 2014;65:844–8. [CrossRef](#)
10. Koc F, Kalay N, Kilci H, Ceyhan K, Celik A, Kadi H, et al. The relationship between renal functions and thrombolysis in myocardial infarction frame count in patients with slow coronary flow. *Kaohsiung J Med Sci* 2011;27:55–8. [CrossRef](#)
11. Beltrame JF. Defining the coronary slow flow phenomenon. *Circ J* 2012;76:818–20. [CrossRef](#)