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Correlation between coronary slow flow phenomenon and Cystatin C

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Abstract: **Our study was to investigate the factors relating to the coronary slow flow phenomenon (CSFP) and to observe the changes of Cystatin C (CysC) level in patients with coronary slow flow phenomenon (CSFP) and clinical predictive value. The CysC levels were examined. The data of patients with coronary angiography were collected. The proportion of male in the CFSP group was significantly higher than the other two groups ($p<0.05$). The age and creatinine level were significantly lower than the other two groups ($p<0.05$). The level of cystatin C, uric acid and proportion of smoking history in patients with CSFP was higher than that in normal group and lower than that in mild stenosis group ($p<0.05$). Cystatin C was an independent risk factor for CSFP (OR>1), while uric acid and history of smoking are not related to CSFP. In the CSFP group, LAD, LCX and appears RCA were 75.36%, 68.12% and 23.91%, respectively. There were no significant differences in gender, age, cystatin C, UA, CREA, UREA, and smoking history among the different vessels in the CSFP group ($P>0.05$). Serum cystatin C level is associated with the occurrence and development of CSFP, and it can be the predictor of CSFP.**

Keywords: Coronary slow flow phenomenon; Cystatin C; Coronary angiography

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1. Introduction

Coronary slow flow phenomenon (CSFP) can delaye distal vessel contrast opacification without evidence of obstructive epicarcial CAD, with the exclusion of no-reflow phenomenon, coronary emboli, coronary ectasia and exogenous vasoconstrictor administration[1]. It was first reported by Tambe[2] in 1972, referring to the slow flow in coronary artery without stenosis, sputum, dilation or other temperamental heart disease. Cystatin C has been used to estimate the damage to microcirculation in kidneys. In recent studies, correlation between CysC level and cardiovascular diseases is detected. This study investigated the possible association between CysC and microcirculation lesions by measuring serum cystatin C level in patients with slow coronary flow. At present, the pathogenesis of coronary slow flow phenomenon remains unknown. Some studies suggest that the possible pathogenesis includes small vessel disease, endothelial dysfunction, subclinical atherosclerosis, inflammatory reaction, anatomical factors, systemic vascular disease, etc.[3]. Therefore, exploring the mechanism and risk factors of its occurrence and development has important clinical significance for improving the prognosis of patients and improving their quality of life.

2. Materials and methods

2.1. Materials

Retrospective analysis of patients in the affiliated Hospital of Qingdao University from June 2013 to April 2018 for angina were conducted. According to TIMI blood flow classification, 138 patients were defined as the CSFP Group. A total of 261 patients were diagnosed coronary angiography in the same period. According to the angiographic results, 156 patients had no obvious stenosis (normal angiography group), and 95 patients had 20%-49% stenosis (mild stenosis group).

A total of 389 patients with coronary angiography at the Affiliated Hospital of Qingdao University from June 2013 to April 2018 were enrolled. According to the angiographic results, all cases were divided into CSFP group (n=138), normal group (n=156) and mild stenosis group (n=95). Collect general information and related data of these patients and observe the serum level of serum cystatin C, uric acid and creatinine.

2.2. Clinical data

Relevant clinical data of all subjects including gender, age, smoking history, past medical history etc. were collected. All patients were banned from eating for more than 8 hours before 5ml of venous blood were collected. Serum cystatin C, uric acid (UA) and serum creatinine (CREA) levels were determined by immunoturbidimetry. All the above operations were performed by the staff from the Affiliated Hospital of Qingdao University.

2.3. Statistical methods

The SPSS21.0 statistical software was used to for the data analysis. The data was described by the number of cases (n). The difference between the groups was statistically inferred by the x^2 test. The measurement data were described by $\bar{x} \pm s$. The Komogorov-Smirnov normality analysis showed P<0.05, that is, the data did not conform to the normal distribution, so the comparison between groups was analyzed by nonparametric rank sum test. The difference was statistically significant at P<0.05. To further examine the relevance between the observed indicators and the occurrence of CSFP, and to search for the correlation between them, we used multiple logistic regression analysis.

3. Results

3.1. Comparison of CSFP, normal and mild stenosis groups

There were significant differences in gender ratio, age, cystatin C, CREA, and smoking history among the three groups (P<0.05). Comparison of CSFP, normal and mild stenosis groups. There were significant differences in gender ratio, age, cystatin C, CREA, and smoking history among the three groups (P<0.05). The proportion of smoking history, level of cystatin C and UA in the CSFP group were lower than those index in the mild stenosis group and higher than those index in the normal group(P<0.05). The age and CREA of patients with CSFP were significantly lower than that in the other two groups (P<0.05). The male ratio was higher than the other two groups (P<0.05). The CREA of the normal group was significantly lower than that of the mild stenosis group (Table 1).

Table 1. Indicators of three groups ($\bar{x} \pm s$)

	CSFP(n=138)	Normal(n=156)	Mild stenosis(n=95)	P
gender(M/F)	81/57(58.70%/41.30%)	56/100[a](35.90%/64.10%)	55/40[ab](57.89%/42.11%)	0.000
Age	58.986±9.497	61.705±8.562[a]	63.537±9.560[ab]	0.000
Cys C(mmol/L)	0.872±0.179	0.815±0.172[a]	0.881±0.179[ab]	0.010
UA(mmol/L)	322.485±88.498	297.357±82.452[a]	325.221±80.180[ab]	0.004
CREA(mmol/L)	65.647±19.384	77.083±65.918[a]	79.211±22.644[ab]	0.000
Smoking history(Y/N)	52/86 (37.68%/62.32%)	35/121[a] (22.44%/77.56%)	39/56[ab] (69.64%/30.36%)	0.002

[a]compared with CSFP group P＜0.05; [b]:compared with normal group P＜0.05.

3.2. Comparison of blood vessels in CSFP

In CSFP, the proportion of LAD was higher (75.36%), followed by LCX (68.12%), and the proportion of RCA was the least (23.91%), (Table 2).

Table 2. Comparison of blood vessels in CSFP(n=138)

vessel	n	%
LAD	104	75.36
LCX	94	68.12
RCA	33	23.91

3.3. Comparison of blood vessel numbers in CSFP group

In the CSFP group, cases of slow flow vessel number = 1 was 56 (40.58%), cases of number = 2 was 49 (35.51%), and cases of number = 3 was 33 (23.91%). There were no significant differences in gender, age, cystatin C, uric acid, CREA, and smoking history among the different blood vessels in the slow blood flow group (P>0.05), (Table 3).

3.4. Multiple logistic regression analysis of risk factors in CSFP group

Logistic regression results showed that there was a significant correlation between male, age, cystatin C, and creatinine and CSFP (P<0.05), and cystatin C was an independent risk factor forCSFP (OR>1). There was no significant correlation between uric acid, history of smoking and CSFP (Table 4).

Table 3. Comparison of slow flow vessel numbers in CSFP group ($\bar{x} \pm s$)

	vessel=1(n=56)	vessel=2(n=49)	vessel=3(n=33)	X^2/Z	P
Gender(M/F)	32/24	29/20	20/13	0.110[*]	0.946
Age	59.661±8.890	57.816±10.479	59.576±9.073	0.653[#]	0.722
CysC(mmol/L)	0.852±0.145	0.871±0.185	0.908±0.217	1.235[#]	0.539

UA(mmol/L)	310.479±84.009	332.239±80.344	328.376±106.225	1.882#	0.390
CREA(mmol/L)	63.991±18.122	65.696±19.675	68.385±21.238	1.009#	0.604
Smoking history(Y/N)	23/33	17/32	12/21	0.485*	0.785

*: x^2 test; #:rank sum test

Table 4. Multiple logistic regression analysis

		B	Standard error	Wald	P	OR	95%CI	
							min	max
CSFP	Gender	-0.736	0.195	14.216	0.000	0.479	0.327	0.702
	Age	-0.301	0.140	4.621	0.032	0.740	0.562	0.974
	CysC	0.314	0.147	4.553	0.033	1.369	1.026	1.826
	UA	0.141	0.153	0.843	0.358	1.151	0.852	1.555
	Crea	-1.848	0.322	32.923	0.000	0.157	0.084	0.296
	Smoking history	0.083	0.78	0.219	0.640	1.087	0.767	1.540

B: Coefficient estimation; Wald: Chi-square value; OR: Advantage ratio; CI: Confidence interval.

4. Discussion

CSFP is defined as a non-coronary obstructive lesion with delayed coronary artery filling. There are two criteria for definition. One method is basis on TIMI blood flow grading to judge TIMI blood flow. Level 2 covers the phenomenon of distal vascular filling delay, which requires 3 or more cardiac cycles during the coronary angiography. Another method was proposed by Gibson[4] which is to use the TIMI blood flow frame count to evaluate coronary blood flow. If the corrected TIMI blood flow frame count greater than or equal to 27 frames, CSFP could be diagnosed. During more than forty years since its first description, many studies have been performed concerning its frequency, etiology and pathogenesis[11-14].

During more than forty years since its first description, many studies have been performed concerning its frequency, etiology, and pathogenesis.

CysC is antagonistic to cysteine protease. They are in a state of dynamic equilibrium in vivo. CysC has a constant daily secretion and, due to its small molecular weight (13 kD), is almost completely taken up by epithelial cells in the proximal convoluted tubules and is not affected by diet, height, weight, age, malignancy, etc.[5]. In recent years, studies have shown that CysC not only reflect early glomerular injury, but also predict the prognosis of cardiovascular disease. Cys C level changing suggests coronary plaque load level endothelial destruction, inflammatory response, and microthrombus formation[6]. It is generally believed that higher levels of CysC may be associated with stroke, coronary heart disease, acute coronary syndrome, and progressively larger atherosclerotic plaques[7]. At different stages of myocardial infarction, the levels of CysC may elevate, normal, and decrease, which means a shift in the secretion, depletion, and activation of cardiovascular disease[10]. During the development of atherosclerosis, CysC levels show the level of inflammatory response in the body. The increase of CysC suggests that inflammatory factors are activated in the body, blood homocysteine levels are elevated, endothelial cells are damaged, endothelial dysfunction induced, and the imbalance between the circulating coagulation and fibrinolytic system, microvascular remodeling, resulting in increasing of microcirculatory vascular resistance and thrombosis, leading to slow coronary flow[8]. In our study, the level of cystatin C in the CSFP group was between the normal and mild stenosis groups. So it suggested that patients with CSFP did not form atherosclerotic plaque in epicardial coronary, the endothelial damage and inflammatory reactions have already existed in the body. Logistic regression analysis showed that CSFP patients had a higher proportion of male and lower mean age than those with normal angiography and mild stenosis, and their serum creatinine levels were significantly lower than the other two groups. Since creatinine levels are largely affected by age. The lower levels of serum creatinine may be associated with lower age in patients with slow coronary flow. In the slow blood flow group, the frequency of the left coronary system is significantly higher than that of the right coronary system. Combined with the characteristics of the coronary anatomy, the reason may be due to the large diameter of the left coronary system[9]. According to the flow formula, the same volume of blood per unit time, the larger the tube diameter, the slower the flow rate.

5. Conclusion

Elevated level of CysC, male, young age may be risk factors for coronary slow flow. Serum cystatin C level is associated with the occurrence and

development of CSFP, and it can be the predictor of CSFP. By dynamic monitoring of its level ,we can predict the occurrence, development and prognosis of CSFP. Further research concerning the mechanism of CSFP is needed to improve our view of CSFP.

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References

[1] Beltrame JF. Defining the coronary slow flow phenomenon[J]. Circulation Journal Official Journal of the Japanese Circulation Society, 2012, 76(4):818.

[2] Tambe AA, Demany MA, Zimmerman HA, et al. Angina pectoris and slow flow velocity of dye in coronary arteries--a new angiographic finding[J]. American Heart Journal, 1972, 84(1):66-71.

[3] Wang X, Nie SP. The coronary slow flow phenomenon: characteristics, mechanisms and implications.[J]. Cardiovascular Diagnosis & Therapy, 2011, 1(1):37-43.

[4] Gibson CM , Cannon CP , Daley WL , et al. TIMI Frame Count : A Quantitative Method of Assessing Coronary Artery Flow[J]. Circulation, 1996, 93(5):879-888.

[5] Min W. Multicenter Clinical Study on the Treatment of Children's Tic Disorder with Qufeng Zhidong Recipe[J]. Chinese Journal of Integrative Medicine, 2009, 15(4):254-260.

[6] Niccoli G, Conte M, Bona RD, et al. Cystatin C is associated with an increased coronary atherosclerotic burden and a stable plaque phenotype in patients with ischemic heart disease and normal glomerular filtration rate[J]. Atherosclerosis, 2008, 198(2):373-380.

[7] Triki S, Fekih O, Hellara I, et al. Association between serum cystatin C levels and cardiovascular disease in type 2 diabetic patients[J]. Annales De Biologie Clinique, 2013, 71(4):438-442.

[8] Shi Q, Yang D, Su Y, et al. Covalent functionalization of multi-walled carbon nanotubes by lipase[J]. Journal of Nanoparticle Research, 2007, 9(6):1205-1210.

[9] Wang F. Anatomical observation of ophthalmic artery and branches[J]. Chinese Ophthalmic Research, 2000.

[10] Weiss-Sadan T, Gotsman I, Blum G. Cysteine proteases in atherosclerosis[J]. Febs Journal, 2017, 284(10):1455-1472.

[11] Tanriverdi H, Evrengul H, Kilic ID, Taskoylu O, Dogan G, Alpsoy S. Aortic pressures, stiffness and left ventricular function in coronary slow flow phenomenon[J]. Cardiology, 2010, 116:261-7.

[12] Nurkalem Z, Gorgulu S, Uslu N, Orhan AL, Alper AT, Erer B, et al. Longitudinal left ventricular systolic function is impaired in patients with coronary slow flow[J]. Cardiovasc Imaging, 2009, 25:25-32.

[13] Elsherbiny IA. Left ventricular function and exercise capacity in patients with slow coronary flow[J]. Echocardiography, 2012, 29:158-64.

[14] Baykan M, Baykan EC, Turan S, Gedikli O, Kaplan S , Kiris A, et al. Assessment of left ventricular function and Tei index by tissue Doppler imaging in patients with slow coronary flow[J]. Echocardiography, 2009, 26:1167-72.

