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Coronary Artery Disease

Serum Sphingosine 1 Phosphate Levels in Patients with and without Coronary Collateral Circulation

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Background: Sphingosine 1 phosphate, an active sphingolipid metabolite, functions in both healthy and diseased cardiovascular systems. It has been reported to play a role in angiogenesis and arteriogenesis in various tissues, which are the proposed mechanisms for the development of coronary collateral circulation. To the best of our knowledge, no data exist regarding serum sphingosine 1 phosphate levels and the presence of coronary collateral circulation in the literature. Thus this study aimed to investigate serum sphingosine 1 phosphate levels in patients with and without coronary collateral circulation.

Methods: A total of 140 patients were included (70 with coronary collateral circulation and 70 with normal coronary arteries and stable coronary artery disease without collaterals). Rentrop collateral grade and the number of coronary arteries with collateral circulation were recorded.

Results: Serum sphingosine 1 phosphate levels were higher in the collateral group than in the control group [186.6 (142.3-243.5) μg/l vs. 128.5 (105.0-161.6) μg/l, $p < 0.001$]. Multivariate logistic regression analysis revealed that the presence of multivessel disease, high serum sphingosine 1 phosphate levels and previous history of P2Y12 use were independent predictors of coronary collateral circulation. Median sphingosine 1 phosphate levels in different Rentrop grades in the collateral group were similar, and there was no significant difference in median serum sphingosine 1 phosphate level with a higher number of coronary arteries with collateral circulation.

Conclusions: Our findings demonstrated higher levels of sphingosine 1 phosphate in the patients with coronary collateral circulation.

Key Words: Coronary artery disease • Coronary collateral • Sphingosine 1 phosphate

INTRODUCTION

Coronary artery disease (CAD) is a major cause of morbidity and mortality worldwide.[1] The extension of ischemic myocardium and the severity of permanent left ventricular systolic dysfunction are important prognostic factors for patients with CAD. Appropriate revascularization in stable CAD, early reperfusion in acute coronary syndrome, and prevention of reperfusion injury during myocardial infarction can reduce myocardial damage and dysfunction leading to improved cardiovascular outcomes.[2-4] The presence of coronary collateral circulation (CCC) is another prognostic factor in patients with CAD.[5,6] Many natural artery-to-artery and arteriole-to-arteriole anastomoses are present in healthy tissues. Arteriole-to-arteriole anastomoses can be defined as microvascular collaterals, and coronary collaterals belong to this group. In general, the radius of these collaterals is smaller than 100 μm, but coronary collaterals may have a radius larger than 150 μm in a healthy heart.[7] The possible mechanisms explaining coronary collateral development include angiogenesis (capillary formation by sprouting from preexisting capillaries) and arteriogenesis (remodeling of a preexisting collateral which results in a thicker

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and larger vessel).[8] CCC protects the myocardium during ischemia, but this beneficial effect is not detected in every individual in the same manner because the numbers and diameters of existing collaterals may be different or the rate and grade of collateral development may vary between individuals after the occlusive event. Therefore, it is important to identify genetic, cellular and environmental factors which determine the effectiveness of collateral circulation development.

Sphingosine 1 phosphate (S1P) is an active sphingolipid metabolite that functions in cell motility, cell growth, cytoskeletal organization and the immune system.[9] It is mostly carried by plasma proteins, especially high density lipoprotein (HDL) and albumin.[10] Previous studies have demonstrated that S1P protects the heart from reperfusion injury by stabilizing the mitochondria, and we previously showed a relationship between pre-infarction angina as the surrogate marker of ischemic preconditioning and serum S1P levels.[11-13] In addition to these functions, previous reports have also revealed that S1P may play a crucial role in angiogenesis and arteriogenesis.[14,15] Therefore, S1P may also have cardioprotective effects in coronary collateral development in addition to reducing the reperfusion injury. Thus, understanding the interaction between S1P and CCC may lead to the development of therapeutic angiogenesis. To the best of our knowledge, no previous study has investigated the relationship between the presence of human coronary collaterals and serum S1P levels. Therefore, the goals of this study were to evaluate serum S1P levels in patients with and without CCC, demonstrate serum S1P levels in patients with normal coronary arteries, stable CAD and CCC, and investigate serum S1P levels with regards to CCC grade.

MATERIALS AND METHODS

The protocol of this cross-sectional study was approved by the local ethics committee, and informed consent was obtained from all of the participants. This study was conducted between January 2016 and December 2016. Seventy patients with CCC were included, all of whom had been diagnosed with stable CAD and all had at least 90% stenosis in an epicardial coronary artery with collateral distal blood supply. The patients diagnosed with acute coronary syndrome within the last six months (unstable angina pectoris or myocardial infarction), patients with previous surgical coronary revascularization history, documented significant peripheral artery disease, significant valvular disease, renal or hepatic disease (glomerular filtration rate < 60, proteinuria, elevated hepatic transaminases), chronic inflammatory disease, decompensated heart failure, active infection and malignancy were excluded. After enrolling the cases with CCC, 70 consecutive patients with normal coronary arteries or stable coronary lesions without collateral circulation were included as the control group. The exclusion criteria for the control group were the same as for the CCC group. The clinical and demographic characteristics of the patients were recorded. Blood samples were collected with antecubital vein puncture after coronary angiography. The samples were centrifuged at 4000 rpm for 10 minutes, and the serum was separated and stored at -80 °C. The parameters of serum biochemistry, lipid panel and complete blood count were obtained from local laboratory records. S1P analyses were carried out using Eastbiopharm ELISA (Hangzhou, Zhejiang, PRC) kits; all samples were processed simultaneously. Coronary angiography recordings were assessed by two experienced cardiologists, and the number of coronary arteries with collateral blood supply was recorded. The grading of coronary collaterals was ascertained using the Rentrop classification system as described previously.[16] Multivessel disease was defined as the presence of significant stenosis (≥ 50% diameter obstruction) in ≥ 2 major coronary arteries. SPSS 17.0 software for Windows (SPSS Inc. Chicago, IL) was used for all data analysis. For continuous variables, normality of distribution was tested using the Kolmogorov-Smirnov test. The results were presented as mean ± standard deviation for variables with normal distribution, and as median (interquartile range 25-75) for variables with abnormal distribution. Statistical comparisons of continuous variables were performed using the independent samples *t*-test or Mann-Whitney U test regarding the distribution pattern. Comparisons of categorical variables were performed using the chi-square test. In cases of more than two independent groups, statistical comparisons of median values were performed using the Kruskal-Wallis H test. For the multivariate analysis, the possible factors identified in univariate analysis were

further entered into a logistic regression model to determine the independent predictors of the presence of CCC. Receiver operating characteristic (ROC) curve analysis was used to test whether the S1P level could predict the presence of CCC. A p value < 0.05 was considered to be statistically significant.

RESULTS

A total of 3843 diagnostic coronary angiography procedure were performed during the study period. Of these, 1580 patients had acute coronary syndrome and 241 had a valvular disease or a history of coronary artery bypass grafting surgery. Of the remaining 2022 patients, 748 had normal coronary arteries or irregularities at the coronary wall, and 70 had CCC. The baseline clinical and laboratory parameters of the study groups are shown in Table 1. The patients were significantly older (65 ± 11 vs. 59 ± 12, p = 0.007) and significantly more were male (77.1% vs. 55.7%, p = 0.007) in the collateral group. Serum S1P levels were significantly higher in the collateral group than in the control group [186.6 (142.3-243.5) vs. 128.5 (105.0-161.6), p < 0.001]. Multivessel disease was significantly more common in the patients with CCC (Table 1). Multivariate logistic regression analysis revealed that the presence of multivessel disease was the strongest predictor of the presence of CCC. In addition, high serum S1P levels and the use of P2Y12 were the other independent predictors of the presence of CCC (Table 2). In ROC curve analysis, the cutoff value for S1P, which is a predictor of the presence of CCC, was

Table 1. Baseline characteristics and laboratory parameters of the study patients

	Overall (n = 140)	Coronary collateral present (n = 70)	Coronary collateral absent (n = 70)	p
Age, years	62 ± 12	65 ± 11	59 ± 12	0.007
Male, n (%)	93 (66.4)	54 (77.1)	39 (55.7)	0.007
Hypertension, n (%)	57 (40.7)	29 (41.4)	28 (40.0)	0.86
Smoking, n (%)	47 (33.6)	22 (31.4)	25 (35.7)	0.59
Diabetes mellitus, n (%)	40 (28.6)	21 (30.0)	19 (27.1)	0.70
Hyperlipidemia, n (%)	31 (22.1)	17 (24.3)	14 (20.0)	0.54
Fasting blood glucose, mmol/l	5.82 (3.82-7.21)	6.21 (5.49-7.60)	5.71 (5.27-6.71)	0.064
Creatinine, μmol/l	88.4 (79.5-103.4)	88.4 (79.5-106.0)	84.8 (76.0-99.0)	0.087
Total cholesterol, mmol/l	4.79 ± 1.21	4.61 ± 1.24	4.97 ± 1.19	0.081
HDL, mmol/l	1.06 (0.88-1.21)	1.03 (0.85-1.21)	1.08 (0.90-1.24)	0.095
LDL, mmol/l	2.95 ± 1.03	2.79 ± 1.03	3.10 ± 1.01	0.066
Triglyceride, mmol/l	1.48 (1.06-2.05)	1.51 (1.09-2.27)	1.45 (0.99-2.28)	0.38
Hemoglobin, gr/dl	13.9 (12.8-14.9)	13.8 (12.1-14.7)	14 (12.9-15.0)	0.14
White blood cell count, $*10^3$	8.1 (6.8-9.6)	8.1(6.7-9.4)	8.1 (7.0-10.3)	0.51
Platelet count, $*10^3$	241 ± 64	237 ± 59	244 ± 59	0.53
Sphingosine 1 phosphate, μg/l	150.5 (115.7-213.4)	186.6 (142.3-243.5)	128.5 (105.0-161.6)	< 0.001
Number of diseased vessel, n (%)				< 0.001
0	38 (27.1)	0 (0)	38 (54.3)	
1	24 (17.1)	11 (15.7)	13 (18.6)	
2	43 (30.7)	33 (47.1)	10 (14.3)	
3	35 (25.0)	26 (37.1)	9 (12.9)	
ACEI/ARB, n (%)	83 (59.3)	48 (68.6)	35 (50)	0.025
Aspirin, n (%)	73 (52.1)	43 (61.4)	30 (42.9)	0.028
P2Y12 inhibitor, n (%)	25 (17.9)	17 (24.3)	8 (11.4)	0.047
Statin, n (%)	77 (55)	45 (64.3)	32 (45.7)	0.027
CCB, n (%)	35 (25)	16 (22.9)	19 (27.1)	0.558
OAD, n (%)	36 (25.7)	18 (25.7)	18 (25.7)	1.00

ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin II receptor blocker; CCB, calcium channel blocker; HDL, high density lipoprotein; LDL, low density lipoprotein; OAD, oral anti-diabetic.

Table 2. Univariate and multivariate logistic regression analysis showing the independent predictors of coronary collateral presence

	Univariated model				Multivariated model			
	OR	95% CI		p	OR	95% CI		p
		Lower	Upper			Lower	Upper	
Age	1.042	0.010	1.074	0.009				
Gender (male)	2.683	1.292	5.570	0.008				
Fasting blood glucose	1.003	0.997	1.010	0.31				
Creatinine	2.992	0.706	12.682	0.13				
Total cholesterol	0.994	0.986	1.001	0.083				
HDL	0.973	0.943	1.003	0.081				
LDL	0.992	0.983	1.001	0.068				
S1P (μg/l)	1.003	1.000	1.005	0.024	1.003	1.001	1.006	0.018
Presence of multivessel disease	14.397	6.267	33.076	< 0.001	15.508	6.315	38.082	< 0.001
ACEI/ARB	2.182	1.096	4.344	0.026				
Aspirin	2.123	1.081	4.174	0.029				
P2Y12 inhibitor	2.486	0.994	6.212	0.052	3.301	1.035	10.526	0.044
Statin	2.010	1.023	3.949	0.043				

ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin II receptor blocker; CI, confidence interval; HDL, high density lipoprotein; LDL, low density lipoprotein; OR, odds ratio; S1P, sphingosine 1 phosphate.

141.2 μg/l with 75.7% sensitivity and 60% specificity (area under the ROC curve: 0.714, 95% confidence interval 0.628-0.799, p < 0.001) (Figure 1).

We investigated whether serum S1P levels changed with Rentrop collateral grade and whether there was a difference in serum S1P levels regarding the number of coronary arteries with collateral supply. S1P levels of the patients with grade 1, grade 2 and grade 3 collateral circulation were significantly higher than the levels of the patients in the control group, however they were similar between the groups of collateral grades (Figure 2). In our study population, 52 patients had collateral circulation in a single coronary or side branch territory, 14 patients had collateral circulation in two coronary and/or side branch territories and 4 patients had collateral circulation in three coronary and/or side branch territories. The median serum S1P levels of these groups were 158.6 μg/l, 200.7 μg/l and 222.3 μg/l, respectively. All of these values were significantly higher in the collateral group than in the control group, but there was no significant difference between the groups in terms of the number of coronary arteries with collateral circulation

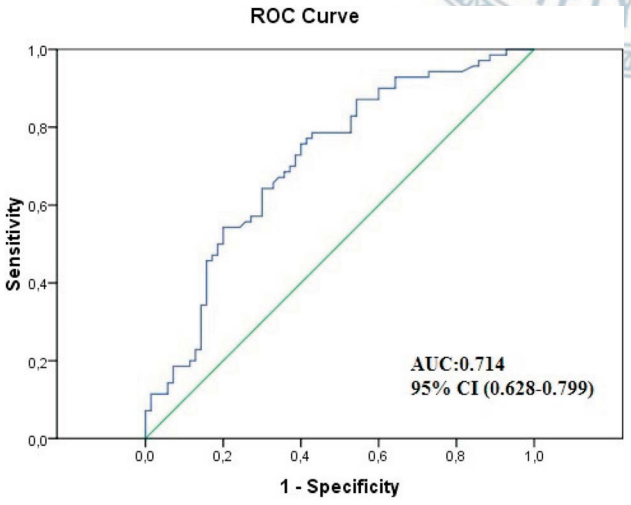

Figure 1. *ROC curve analysis for sphingosine 1 phosphate to predict the presence of coronary collateral circulation.*

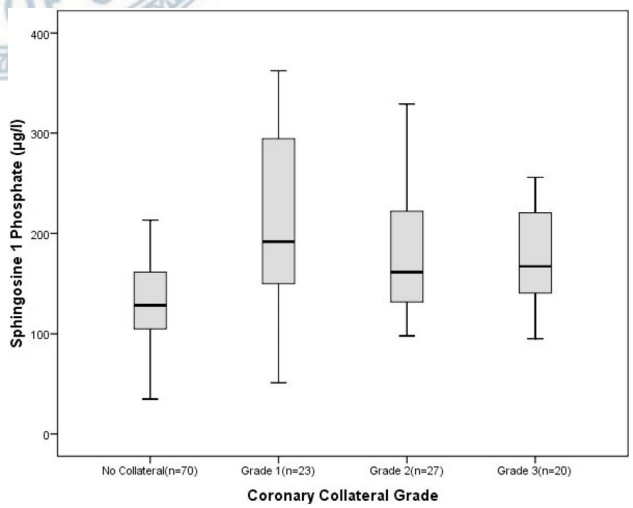

Figure 2. *Sphingosine 1 phosphate levels in control group and Rentrop collateral grade 1, 2 and 3 groups.*

(Figure 3). Our control group consisted of patients with normal coronary arteries (n = 37) and stable CAD (n = 33), and serum S1P levels were similar between these patients (median S1P level of the patients with stable CAD of 128.3 μg/l, and 131.5 μg/l for the patients with normal coronary arteries). Serum S1P levels of the patients with CCC were significantly higher than those of the patients with stable CAD or normal coronary arteries (CCC group vs. stable CAD group: p = 0.001; CCC group vs. normal coronary artery group p < 0.001).

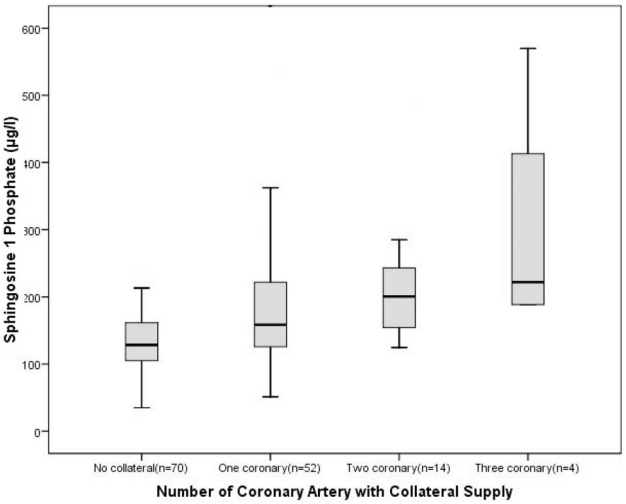

Figure 3. *Sphingosine 1 phosphate levels in control patients and in patients with collateral circulation in one, two or three vessels.*

DISCUSSION

Our results showed that serum S1P levels were significantly higher in the patients with CCC than in the patients with stable CAD and normal coronary arteries. A significant and independent relationship was found between the presence of CCC and serum S1P levels. The other independent predictor of CCC was the presence of multivessel disease. Although serum S1P levels were significantly higher in the patients with CCC, Rentrop collateral grade and the number of coronary arteries with collateral circulation did not significantly differ.

S1P is an active agent of sphingolipid metabolism and seems to be an emerging mediator of both healthy and diseased cardiovascular systems. The source of circulating S1P is largely red blood cells and endothelial cells.[17] HDL and albumin are the most important transporters of S1P in the circulation.[10] Recently, the cardioprotective effects of S1P have been investigated extensively. S1P has been shown to function in the regulation of endothelial permeability, blood pressure regulation and vascular myogenic tonus.[18-20] Experimental studies have demonstrated that S1P protects myocytes from ischemia/reperfusion injury and reduces the infarct size by activating ischemic preconditioning pathways.[21] Clinically, the only sign of ischemic preconditioning is the presence of preinfarction angina, and we previously demonstrated a possible relationship between preinfarction angina and serum S1P levels.[13] S1P is thought to contribute to several cardioprotective effects of HDL such as vasodilation, anti-inflammatory and antioxidant effects.[22] Another suggested cardioprotective effect of S1P is through reducing inflammatory damage and fibrosis in heart failure.[23]

In addition to the aforementioned cardiovascular effects, S1P seems to play a role in angiogenesis and arteriogenesis in different tissues. Soleimani et al. demonstrated that S1P induces neoangiogenesis in ovarian transplants,[24] and many reports have described the role of S1P in tumor angiogenesis.[25] Sefcik et al. observed an expansion in the luminal diameters of the arterioles along with sustained S1P release in bone defect healing.[15] These data suggest that S1P may play a role in the development of coronary collaterals. Our findings suggest that high serum S1P levels may partly play a role in the development of human CCC. We found that a high serum S1P level was an independent predictor of the presence of CCC. However, we did not detect any relationship between serum S1P levels and Rentrop collateral grade or increased number of coronary arteries with collateral circulation; thus, our findings indicate that, even if S1P maybe involved in the development of CCC, there must be some additional factors affecting the grade and quantity of coronary collateral development. Five different G coupled receptors for S1P binding called S1P receptor (S1PR) 1-5 have been identified in various tissues.[26] S1PR1 is the most common S1P receptor on the surface of endothelial cells and functions in vasculogenesis and angiogenesis.[27] The major carrier of S1P in the circulation is the Apolipoprotein M part of HDL, and the second most common carrier is albumin. It is unclear whether or not these carriers control S1P-S1PR1 interactions, and it is also unclear whether or not other S1PR

types have any effect on coronary collateral development. Although there was no association between S1P levels and collateral grade in our study which seems to decrease the importance of S1P in coronary collateral development, we believe that it would not be appropriate to make a firm conclusion about the role of S1P in coronary collateral development before the above mentioned issues have been studied.

The other finding of our study is the independent association between multivessel disease and CCC. This finding is consistent with previous studies. McMurty et al. demonstrated that high risk anatomy (two vessel, three vessel and left main disease) was one of the clinical correlates of angiographically apparent coronary collaterals.[28] Multivessel disease has been reported to be an independent determinant of collaterals in different studies.[29-31] It is known that ischemia plays a critical role in the development of CCC.[32-35] In ischemic myocardium, various growth factors involved in the development of collateral formation are expressed.[36,37] Ischemic myocardial mass in patients with multivessel disease is expected to be higher, and this may result in increased levels of growth factors. This is supported by a study from Fleisch et al., who demonstrated higher vascular endothelial growth factor concentrations with more extended CAD.[38] We also found that a previous history of P2Y12 use was an independent predictor of CCC development. Few studies have reported about the effect of P2Y12 inhibitors on CCC development. Hoefer et al. found a neutral effect on arteriogenesis and collateral development in an experimental study.[36]

Limitations

In this study, S1P ELISA kits were used to detect serum S1P levels. Only albumin-bound S1P can be detected with this method. HDL-bound S1P or the sum of HDL- and albumin-bound S1P levels may have yielded different results. Another important limitation of our study is the small sample size, and a study with more patients may provide more definite results.

CONCLUSIONS

This study suggests that S1P, which is thought to reduce reperfusion injury in acute myocardial infarction and contribute to the cardioprotective effects of HDL, is increased in patients with CCC. This finding supports the hypothesis that S1P may play a role in the development of CCC. This hypothesis should be tested in further studies.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

REFERENCES

1. Gaziano JM. *Global burden of cardiovascular disease*. In: Libby. P, Bonow. RO, Mann. DL, et al., editors. Braunwald's Heart Disease. 8 ed. Philedelphia: Saunders Elsevier; 2008. p. 1-23.
2. Bulluck H, Yellon DM, Hausenloy DJ. Reducing myocardial infarct size: challenges and future opportunities. *Heart* 2016;102:341-8.
3. De Bruyne B, Fearon WF, Pijls NH, et al. Fractional flow reserve-guided PCI for stable coronary artery disease. *The New England Journal of Medicine* 2014;371:1208-17.
4. O'Gara PT, Kushner FG, Ascheim DD, et al. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Journal of the American College of Cardiology* 2013;61:e78-140.
5. Antoniucci D, Valenti R, Moschi G, et al. Relation between preintervention angiographic evidence of coronary collateral circulation and clinical and angiographic outcomes after primary angioplasty or stenting for acute myocardial infarction. *The American Journal of Cardiology* 2002;89:121-5.
6. Meier P, Gloekler S, Zbinden R, et al. Beneficial effect of recruitable collaterals: a 10-year follow-up study in patients with stable coronary artery disease undergoing quantitative collateral measurements. *Circulation* 2007;116:975-83.
7. Faber JE, Chilian WM, Deindl E, et al. A brief etymology of the collateral circulation. *Arteriosclerosis, Thrombosis, and Vascular Biology* 2014;34:1854-9.
8. Koerselman J, van der Graaf Y, de Jaegere PP, et al. Coronary collaterals: an important and underexposed aspect of coronary artery disease. *Circulation* 2003;107:2507-11.
9. Karliner JS. Sphingosine kinase and sphingosine 1-phosphate in

the heart: a decade of progress. *Biochimica et Biophysica Acta* 2013;1831:203-12.
10. Kihara A, Igarashi Y. Production and release of sphingosine 1-phosphate and the phosphorylated form of the immunomodulator FTY720. *Biochimica et Biophysica Acta* 2008;1781:496-502.
11. Karliner JS, Honbo N, Summers K, et al. The lysophospholipids sphingosine-1-phosphate and lysophosphatidic acid enhance survival during hypoxia in neonatal rat cardiac myocytes. *J Mol Cell Cardiol* 2001;33:1713-7.
12. Vessey DA, Li L, Honbo N, et al. Sphingosine 1-phosphate is an important endogenous cardioprotectant released by ischemic pre- and postconditioning. *American Journal of Physiology Heart and Circulatory Physiology* 2009;297:H1429-35.
13. Kiziltunc E, Abaci A, Ozkan S, et al. The relationship between pre-infarction angina and serum sphingosine-1-phosphate levels. *Acta Cardiol Sin* 2014;30:546-52.
14. Qi X, Okamoto Y, Murakawa T, et al. Sustained delivery of sphingosine-1-phosphate using poly(lactic-co-glycolic acid)-based microparticles stimulates Akt/ERK-eNOS mediated angiogenesis and vascular maturation restoring blood flow in ischemic limbs of mice. *Eur J Pharmacol* 2010;634:121-31.
15. Sefcik LS, Petrie Aronin CE, Wieghaus KA, et al. Sustained release of sphingosine 1-phosphate for therapeutic arteriogenesis and bone tissue engineering. *Biomaterials* 2008;29:2869-77.
16. Rentrop KP, Cohen M, Blanke H, et al. Changes in collateral channel filling immediately after controlled coronary artery occlusion by an angioplasty balloon in human subjects. *Journal of the American College of Cardiology* 1985;5:587-92.
17. Sasset L, Zhang Y, Dunn TM, et al. Sphingolipid de novo biosynthesis: a rheostat of cardiovascular homeostasis. *Trends in Endocrinology & Metabolism* 2016;27:807-19.
18. Bolz SS, Vogel L, Sollinger D, et al. Sphingosine kinase modulates microvascular tone and myogenic responses through activation of RhoA/Rho kinase. *Circulation* 2003;108:342-7.
19. Cantalupo A, Zhang Y, Kothiya M, et al. Nogo-B regulates endothelial sphingolipid homeostasis to control vascular function and blood pressure. *Nat Med* 2015.
20. Christensen PM, Liu CH, Swendeman SL, et al. Impaired endothelial barrier function in apolipoprotein M–deficient mice is dependent on sphingosine-1-phosphate receptor 1. *The FASEB Journal* 2016;30:2351-9.
21. Means CK, Xiao CY, Li Z, et al. Sphingosine 1-phosphate S1P2 and S1P3 receptor-mediated Akt activation protects against in vivo myocardial ischemia-reperfusion injury. *American Journal of Physiology-Cell Physiology* 2007;61:H2944.
22. Sattler KJ, Elbasan S, Keul P, et al. Sphingosine 1-phosphate levels in plasma and HDL are altered in coronary artery disease. *Basic Res Cardiol* 2010;105:821-32.
23. Zhang Y, Huang Y, Cantalupo A, et al. Endothelial Nogo-B regulates sphingolipid biosynthesis to promote pathological cardiac hypertrophy during chronic pressure overload. *JCI Insight* 2016;1.
24. Soleimani R, Heytens E, Oktay K. Enhancement of neoangiogenesis and follicle survival by sphingosine-1-phosphate in human ovarian tissue xenotransplants. *PLoS One* 2011;6:e19475.
25. Takuwa Y, Du W, Qi X, et al. Roles of sphingosine-1-phosphate signaling in angiogenesis. *World J Biol Chem* 2010;1:298-306.
26. Proia RL, Hla T. Emerging biology of sphingosine-1-phosphate: its role in pathogenesis and therapy. *J Clin Invest* 2015;125:1379-87.
27. Xiong Y, Hla T. S1P control of endothelial integrity. *Curr Top Microbiol Immunol* 2014;378:85-105.
28. McMurtry MS, Lewin AM, Knudtson ML, et al. The clinical profile and outcomes associated with coronary collaterals in patients with coronary artery disease. *Can J Cardiol* 2011;27:581-8.
29. Nathoe HM, Koerselman J, Buskens E, et al. Determinants and prognostic significance of collaterals in patients undergoing coronary revascularization. *Am J Cardiol* 2006;98:31-5.
30. Hsu PC, Su HM, Juo SH, et al. Influence of high-density lipoprotein cholesterol on coronary collateral formation in a population with significant coronary artery disease. *BMC Res Notes* 2013;6:105.
31. Hsu PC, Su HM, Lee HC, et al. Coronary collateral circulation in patients of coronary ectasia with significant coronary artery disease. *PLoS One* 2014;9:e87001.
32. Seiler C, Stoller M, Pitt B, et al. The human coronary collateral circulation: development and clinical importance. *Eur Heart J* 2013;34:2674-82.
33. Cankurt T, Acar B, Aydin S, et al. ALCAPA syndrome and atrial septal defect in a 68-year-old woman: an extremely rare congenital association. *Acta Cardiol Sin* 2017;33:447-9.
34. Chou RH, Lai CH, Lu TM. Side-branch and coaxial intravascular ultrasound guided wire re-entry after failed retrograde approach of chronic total occlusion intervention. *Acta Cardiol Sin* 2016;32:363-6.
35. Lee CK, Chen YH, Lin MS, et al. Retrograde approach is as effective and safe as antegrade approach in contemporary percutaneous coronary intervention for chronic total occlusion: a Taiwan single-center registry study. *Acta Cardiol Sin* 2017;33:20-7.
36. Schirmer SH, van Nooijen FC, Piek JJ, et al. Stimulation of collateral artery growth: travelling further down the road to clinical application. *Heart* 2009;95:191-7.
37. Fujita M, Ikemoto M, Kishishita M, et al. Elevated basic fibroblast growth factor in pericardial fluid of patients with unstable angina. *Circulation* 1996;94:610-3.
38. Fleisch M, Billinger M, Eberli FR, et al. Physiologically assessed coronary collateral flow and intracoronary growth factor concentrations in patients with 1- to 3-vessel coronary artery disease. *Circulation* 1999;100:1945-50.