Int J Clin Exp Med 2019;12(5):5750-5755
www.ijcem.com /ISSN:1940-5901/IJCEM0089310

Original Article

Changes of plasma homocysteine and hypersensitive C-reactive protein expression in patients with coronary heart disease and their relationship

Rongsheng Bu[1], Yuewu Lin[2], Xinqing Du[1]

[1]*Department of Cardiology, Zone Two, Second Affiliated Hospital of Fujian Medical College, Quanzhou, Fujian, China;* [2]*Cadre Ward of Zhangzhou Hospital Affiliated to Fujian Medical University, Quanzhou, Fujian, China*

Received December 2, 2018; Accepted January 9, 2019; Epub May 15, 2019; Published May 30, 2019

Abstract: Plasma homocysteine (Hcy) and C-reactive protein (CRP) levels are closely related to atherosclerosis. In this study, patients with coronary atherosclerotic heart disease were selected to examine changes of plasma Hcy and CRP expression levels and to analyze their relationship. Coronary atherosclerotic heart disease patients in our hospital were selected as the experimental group and healthy subjects in the same period were treated as the control group. The levels of serum Hcy and hs-CRP were tested and compared in coronary heart disease patients with different clinical types, vascular lesions, and coronary stenosis. The relationship among serum Hcy, hs-CRP, and coronary artery stenosis score was analyzed. The levels of serum Hcy and hs-CRP in SAP, UAP, and AMI patients were higher than those in the control group. The levels of serum Hcy and hs-CRP gradually increased among SAP, UAP, and AMI patients ($P < 0.05$). The levels of serum Hcy and hs-CRP gradually upregulated in single vessel disease group, double vessels disease group, and multi-vessel disease group ($P < 0.05$). The levels of serum Hcy and hs-CRP gradually elevated in patients with mild, moderate, severe stenosis, and entirely occluded ($P < 0.05$). Serum Hcy, hs-CRP, and coronary artery stenosis score exhibited positive correlation with each other ($P < 0.05$). Hcy and hs-CRP increased in coronary heart disease patients with more numbers of the pathological coronary vessels and severe coronary artery stenosis. Serum Hcy, hs-CRP, and coronary artery stenosis score exhibited positive correlation with each other.

Keywords: Homocysteine, high-sensitive C-reactive protein, coronary heart disease

Introduction

The incidence of cardiovascular and cerebrovascular diseases in China gradually increased with society development. It has become a serious threat to human health, which is mainly caused by atherosclerosis. The risk factors inducing atherosclerosis include hypertension, hyperlipidemia, and diabetes, etc. [1]. Coronary atherosclerotic heart disease is a common cardiovascular disease in the clinic with increased incidence, which is mainly caused by coronary atherosclerosis. In the diagnosis of coronary heart disease, previous studies have considered that coronary angiography is the gold standard. However, coronary angiography is an invasive method with high price. In addition, some patients are allergic to the contrast agent, and there is a certain risk in the operation process, resulting in the clinical application limited. Therefore, finding sensitive, safe, and specific inspection methods is important [2].

Atherosclerosis is a chronic inflammatory disease. Inflammation can induce and promote the instability of atherosclerotic plaque, thus playing an important role in the development process of atherosclerosis [3]. C-reactive protein (CRP) is a key inflammatory marker that is mainly synthesized by the liver. It is an acute non-specific marker involved in systemic inflammatory response and one of the most risk predictor of cardiovascular events widely used in coronary heart disease examination [4]. Plasma homocysteine (Hcy) is closely related to cardiovascular and cerebrovascular disease. Its level exhibits a certain correlation with the occurrence and development of atherosclerosis. High level of Hcy produces oxygen free radicals due to their own oxidation, resulting in vascular

endothelial cell damage. It further injuries the protein and induces enzyme-related receptor dysfunction, thereby activating protein kinase C, promoting c-Fos and c-Myc expression in vascular endothelial cells, and participating in the development of coronary atherosclerotic heart disease [5]. Systemic arteriosclerosis and thrombosis appear in patients with high Hcy and high cystathionuria, in the early stage, leading to vascular damage [6]. In this study, patients with coronary atherosclerotic heart disease were selected and changes of plasma Hcy and CRP levels were detected to analyze the relationship, which may provide a theoretical basis for the more accurate treatment of coronary atherosclerotic heart disease.

Materials and methods

General information

A total of 100 patients with coronary atherosclerotic heart disease in Second Affiliated Hospital of Fujian Medical College (Fujian, China) from January 2016 to January 2017 diagnosed by coronary angiography were selected. There were 52 males and 48 females with mean age at 51.2±4.7 (35-70) years old. The subjects were divided into stable angina pectoris group (SAP) (34 cases), unstable angina pectoris group (UAP) (36 cases), and acute myocardial infarction group (AMI) (30 cases) according to different clinical types. There were 20 males and 14 females in SAP, 17 males and 19 females in UAP, and 15 males and 15 females in AMI. The subjects were further divided into single-vessel disease group (31 cases), double-vessel disease group (37 cases), and multi-vessel disease group (32 cases) according to the result of coronary arteriography. Another 100 healthy volunteers were enrolled as the control group, including 64 males and 36 females with an average age of 52.3±5.1 (30-70) years. There were no significant differences in gender, age, and other general data between the two groups ($P > 0.05$). The study was approved by the Medical Ethics Committee in Second Affiliated Hospital of Fujian Medical College (Fujian, China) and all the subjects had provided informed consent.

Exclusion criteria: acute myocardial infarction, unstable angina, or cerebrovascular disease within 3 months; III or IV grade heart failure according to the New York Heart Disease Association (NYHA) grade; contrast agent allergy; trauma, ulcers, and surgery in recent time; received stem cell factor, granulocyte colony-stimulating factor, and statins; other heart disease; chronic infectious disease; chronic heart failure; malignancy; autoimmune disease; diabetes; kidney disease; and liver dysfunction.

Experimental methods

Plasma homocysteine (Hcy) level detection: Peripheral venous blood was collected in the EDTA-Na_2 anticoagulant tube. After centrifugation for 15 minutes, the upper plasma was collected and analyzed on automatic biochemical analyzer (Beckman, model AU480, USA) to detect plasma Hcyr. Hyperhomocysteinemia (HHcy) graduation: mild, 16-30 μmol/L; moderate, 30-100 μmol/L; severe, > 100 μmol/L.

Plasma high-sensitivity C-reactive protein (hs-CRP) level detection: Peripheral venous blood was collected in the tube containing sodium citrate. After centrifugation for 15 minutes, the upper plasma was collected and analyzed on Au640 automatic biochemical analyzer (Olympus, Japan) to detect hs-CRP by immuno-turbidimetric method. The kit was purchased from Beckman (USA).

Coronary angiography: Routine coronary angiography was applied to test the coronary stenosis. Coronary atherosclerotic heart disease was diagnosed by coronary artery diameter ≥ 50% stenosis. The cases were divided into single vessel lesion, double-vessel lesion, and multi-vessel lesion according to the number of damaged coronary artery vessels. Left main branch, anterior descending branch, left circumflex artery and branch, and right coronary artery and branch were counted as one lesion, respectively. Coronary artery stenosis 50%-75% was treated as mild, 76%-90% was treated as moderate, 91%-99% was treated as severe, and 100% was treated as complete occlusion.

Coronary stenosis score: The degree of coronary artery stenosis was scored according to Gensini. Gensini score standard: 0 point, no stenosis; 1 point, stenosis ≤ 25%, 2 points, stenosis at 26%-49%; 4 points, stenosis at 50%-74%; 8 points, stenosis at 75%-89%; 16 points, stenosis at 90%-99%; 32 points at 100% [7].

Data analysis

All data analyses were performed on SPSS 17.0 statistical software. The enumeration data

Table 1. Serum Hcy and hs-CRP levels in patients with different clinical types of coronary heart disease

Group	Cases	Hcy (μmol/l)	hs-CRP (mg/l)
Experimental group	100		
SAP	34	11.33±1.27*	12.45±1.62*
UAP	36	15.89±3.26*,#	19.43±4.27*,#
AMI	30	27.32±5.43*,#,&	34.23±5.64*,#,&
Control group	100	5.82±0.67	1.71±0.68

*P < 0.05, compared with control; #P < 0.05, compared with SAP group; &P < 0.05, compared with UAP group.

Table 2. Serum Hcy and hs-CRP levels in coronary heart disease patients with different numbers of vascular lesions

Group	Cases	Hcy (μmol/l)	hs-CRP (mg/l)
Experimental group	100		
Single vessel disease	31	14.84±2.56*	17.25±3.78*
Double vessels disease	37	20.37±4.13*,#	26.24±5.73*,#
Multi-vessel disease	32	26.97±5.32*,#,&	33.97±5.38*,#,&
Control group	100	6.01±1.12	1.68±0.67

*P < 0.05, compared with control; #P < 0.05, compared with single vessel disease group; &P < 0.05, compared with double vessels disease group.

Table 3. Serum Hcy and hs-CRP Levels in coronary heart disease patients with different coronary stenosis.

Group	Cases	Hcy (μmol/l)	hs-CRP (mg/l)
Experimental group	100		
Mild stenosis	21	12.69±1.87*	16.87±2.03*
Moderate stenosis	29	21.07±3.64*,#	26.13±4.76*,#
Severe stenosis	32	27.78±5.04*,#,&	31.82±5.77*,#,&
Occlusion	18	31.02±5.87*,#,&,@	33.08±6.01*,#,&,@
Control group	100	6.12±1.03	1.71±0.59

*P < 0.05, compared with control; #P < 0.05, compared with mild stenosis group; &P < 0.05, compared with moderate stenosis group; @P < 0.05, compared with severe stenosis group.

were compared by χ^2 test, the measurement data were tested by variance analysis, and the correlation was performed using Pearson correlation test. P < 0.05 was considered as statistical significance.

Results

Serum Hcy and hs-CRP levels in patients with different clinical types of coronary heart disease

The levels of serum Hcy and hs-CRP in the experimental group were significantly higher than those in the control group (P < 0.05). The levels of serum Hcy and hs-CRP gradually increased among SAP, UAP, and AMI patients (P < 0.05) (**Table 1**).

Serum Hcy and hs-CRP levels in coronary heart disease patients with different numbers of vascular lesions

The levels of serum Hcy and hs-CRP in the patients with different number of vascular lesions were higher than those in the control group (P < 0.05). The levels of serum Hcy and hs-CRP gradually upregulated in single vessel disease group, double vessels disease group, and multivessel disease group (P < 0.05) (**Table 2**).

Serum Hcy and hs-CRP Levels in coronary heart disease patients with different coronary stenosis

Serum Hcy and hs-CRP in patients with different coronary stenosis were higher than those in the control group (P < 0.05). The levels of serum Hcy and hs-CRP gradually elevated in patients with mild, moderate, severe stenosis, and entirely occlusion (P < 0.05) (**Table 3**).

The relationship among serum levels of Hcy, hs-CRP, and coronary artery stenosis in patients with coronary heart disease

Serum Hcy and hs-CRP levels were positively correlated with coronary artery stenosis (r = 0.739, P < 0.05; r = 0.701, P < 0.05) (**Figures 1** and **2**).

The relationship between serum Hcy and hs-CRP in patients with coronary heart disease

Serum Hcy exhibited a positive correlation with hs-CRP (r = 0.729, P < 0.05) (**Figure 3**).

Discussion

In recent years, the incidence of coronary heart disease gradually increased in China. Coronary atherosclerosis is the pathologic basis of coronary heart disease and a key factor for its development, leading to complete or incomplete occlusion of the coronary artery. Hcy level is closely related to cardiovascular disease and an independent risk factor for cardiovascular

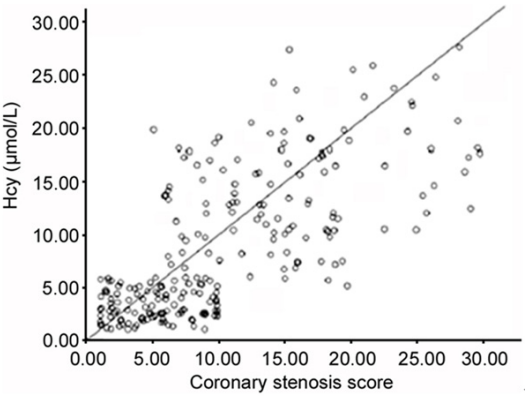

Figure 1. Relationship between serum Hcy level and coronary artery stenosis in patients with coronary heart disease.

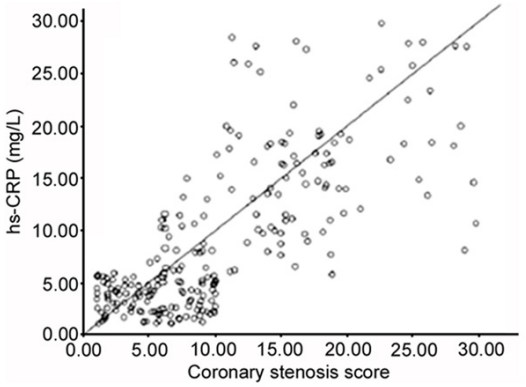

Figure 2. Relationship between serum hs-CRP level and coronary artery stenosis in patients with coronary heart disease.

disease. High levels of Hcy stimulate the vessel wall to damage the arteries, leading to inflammation and arterial plaque formation [8]. hs-CRP is an acute phase protein involved in the inflammatory response. hs-CRP elevates in a short time during inflammation or injury, thus is a sensitive inflammatory marker [9]. This study detected expression of serum Hcy and hs-CRP in patients with coronary heart disease to analyze the relationship between them.

The levels of serum Hcy and hs-CRP in the patients with coronary heart disease were significantly higher than those in the control group. They gradually increased among SAP, UAP, and AMI patients, and reached a peak in AMI group. It has been suggested that hs-CRP and Hcy are key factors in the development of coronary heart disease [10]. Elevated Hcy level is a risk

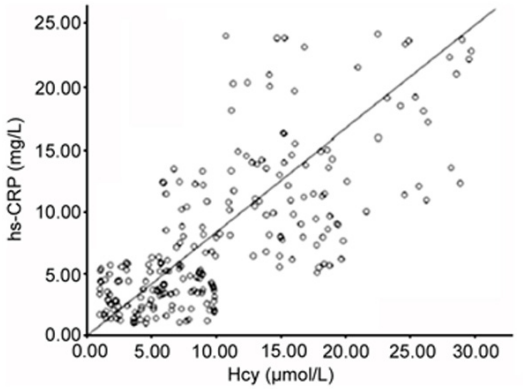

Figure 3. Relationship between serum Hcy level and hs-CRP level in patients with coronary heart disease.

factor for the development of coronary atherosclerosis [11]. hs-CRP is an inflammatory marker involved in the formation and progression of atherosclerotic plaques [12].

The levels of serum Hcy and hs-CRP in patients with different numbers of coronary artery disease were higher than those in control group. The levels of serum Hcy and hs-CRP gradually upregulated in single vessel disease group, double vessels disease group, and multi-vessel disease group. It indicated that high levels of serum Hcy and hs-CRP existed in patients with multiple coronary lesions of coronary artery disease. It was found that Hcy and hs-CRP increased in coronary heart disease patients with varying degrees of coronary artery lesion [13].

Moreover, the levels of serum Hcy and hs-CRP in the patients with different coronary stenosis were higher than those in the control group. The levels of serum Hcy and hs-CRP gradually elevated in patients with mild, moderate, severe stenosis, and entirely occlusion, revealing that high levels of Hcy and hs-CRP appeared in coronary heart disease patients with coronary stenosis, especially in patients with entirely occlusion. Hcy is a metabolite of methionine, which is present in oxidized form in the bloodstream to promote lipid deposition in the arterial wall and atherosclerotic plaque formation. Sustained vascular contraction may cause hypoxia [14, 15]. hs-CRP mainly acts on the vascular wall to activate the complement system, downregulate the synthesis and release of NO, stimulate the release of endothelin-1 and interleu-

kin-6, promote the occurrence of inflammatory response, and facilitate macrophages to devour low-density lipoproteins, leading to vascular injury and coronary heart disease [16, 17].

There was a positive correlation between serum Hcy and hs-CRP levels and coronary artery stenosis. Furthermore, serum Hcy was positively correlated with hs-CRP level. The risk increased 25% when the serum Hcy level elevated 5 μmol/l in CHD patients [18]. There was a significant difference in serum hs-CRP in patients with different types of coronary heart disease and a positive correlation with the severity of coronary artery disease [19, 20]. Serum Hcy level is positively correlated with coronary artery disease [21]. However, how to use more effective means to further assess the incidence of coronary heart disease still needs more in-depth study. In addition, accurate and timely intervention is of great significance to improve the treatment effect of coronary heart disease.

Conclusion

Hcy and hs-CRP increased in coronary heart disease patients with more numbers of the pathological coronary vessels and severe coronary artery stenosis. Serum Hcy, hs-CRP, and coronary artery stenosis score exhibited positive correlation with each other. The level of serum Hcy and hs-CRP can be used as effective indexes for the prediction and evaluation of coronary heart disease. Combined detection is of great significance to predict the occurrence and development of coronary heart disease.

Acknowledgements

This work was supported by General fund of Fujian Provincial Department of Science & Technology (No: 2016J01631).

Disclosure of conflict of interest

None.

Address correspondence to: Dr. Rongsheng Bu, Department of Cardiology, Zone Two, Second Affiliated Hospital of Fujian Medical College, No.34, Zhongshan, North Road, Licheng District, Quanzhou 362000, Fujian, China. Tel: +86-0595-22791001; Fax: +86-0595-22770258; E-mail: caizhan8373-55@163.com

References

[1] Idriss NK, Blann AD, Lip GY. Hemoxygenase-1 in cardiovascular disease. J Am Coll Cardiol 2008; 52: 971-978.

[2] Yildirir A, Acikel S, Ertan C, Aydinalp A, Ozin B, Muderrisoglu H. Effects of lesion complexity on baseline and postprocedural B-type natriuretic peptide levels in patients undergoing percutaneous coronary interventions. Tex Heart Inst J 2007; 34: 282-289.

[3] Porapakkham P, Porapakkham P, Zimmet H, Billah B, Krum H. B-type natriuretic peptide-guided heart failure therapy: a meta-analysis. Arch Intern Med 2010; 170: 507-514.

[4] O'Malley RG, Bonaca MP, Scirica BM, Murphy SA, Jarolim P, Sabatine MS, Braunwald E, Morrow DA. Prognostic performance of multiple biomarkers in patients with non-ST-segment elevation acute coronary syndrome: analysis from the MERLIN-TIMI 36 trial (metabolic rfficiency With Ranolazine for Less Ischemia in non-ST-elevation acute coronary syndromes-thrombolysis in myocardial infarction 36). J Am Coll Cardiol 2014; 63: 1644-1653.

[5] Li X, Zhang X, Wei L, Xia Y, Guo X. Relationship between serum oncostatin M levels and degree of coronary stenosis in patients with coronary artery disease. Clin Lab 2014; 60: 113-118.

[6] Sen U, Mishra PK, Tyagi N, Tyagi SC. Homocysteine to hydrogen sulfide or hypertension. Cell Biochem Biophys 2010; 57: 49-58.

[7] Imhof A, Rothenbacher D, Khuseyinova N, Hoffmeister A, Maerz W, Nauck M, Scharnagl H, Koenig W, Brenner H. Plasma lipoprotein Lp(a), markers of haemostasis and inflammation, and risk and severity of coronary heart disease. Eur J Cardiovasc Prev Rehabil 2003; 10: 362-370.

[8] Zheng JL, Lu L, Hu J, Zhang RY, Zhang Q, Chen QJ, Shen WF. Increased serum YKL-40 and C-reactive protein levels are associated with angiographic lesion progression in patients with coronary artery disease. Atherosclerosis 2010; 210: 590-595.

[9] Terzic J, Grivennikov S, Karin E, Karin M. Inflammation and colon cancer. Gastroenterology 2010; 138: 2101-2114, e2105.

[10] Stankovic S, Majkic-Singh N. Genetic aspects of ischemic stroke: coagulation, homocysteine, and lipoprotein metabolism as potential risk factors. Crit Rev Clin Lab Sci 2010; 47: 72-123.

[11] Aroni K, Ioannidis E, Voudouris S, Yapijakis C. Homocysteinemia-associated anetoderma, in a young woman with anorexia nervosa history. Int J Dermatol 2011; 50: 343-345.

[12] Szalai AJ, McCrory MA, Xing D, Hage FG, Miller A, Oparil S, Chen YF, Mazzone M, Early R, Henry SP, Zanardi TA, Graham MJ, Crooke RM. Inhibiting C-reactive protein for the treatment of cardiovascular disease: promising evidence from rodent models. Mediators Inflamm 2014; 2014: 353614.
[13] McCully KS. Hyperhomocysteinemia and arteriosclerosis: historical perspectives. Clin Chem Lab Med 2005; 43: 980-986.
[14] Jakubowski H. The pathophysiological hypothesis of homocysteine thiolactone-mediated vascular disease. J Physiol Pharmacol 2008; 9: 155-167.
[15] Jacob T, Hingorani A, Ascher E. Evidence for telomerase activation in VSMCs exposed to hyperglycemic and hyperhomocysteinemic conditions. Angiology 2009; 60: 562-568.
[16] Kaminski KA, Tycinska AM, Stepek T, Szpakowicz A, Oledzka E, Dobrzycki S, Musial WJ. Natural history and risk factors of long-term mortality in acute coronary syndrome patients with cardiogenic shock. Adv Med Sci 2014; 59: 156-160.
[17] Jiang C, Zhang H, Zhang W, Kong W, Zhu Y, Zhang H, Xu Q, Li Y, Wang X. Homocysteine promotes vascular smooth muscle cell migration by induction of the adipokine resistin. Am J Physiol Cell Physiol 2009; 297: C1466-1476.
[18] Haim M, Tanne D, Goldbourt U, Doolman R, Boyko V, Brunner D, Sela BA, Behar S. Serum homocysteine and long-term risk of myocardial infarction and sudden death in patients with coronary heart disease. Cardiology 2007; 107: 52-56.
[19] Bassuk SS, Rifai N, Ridker PM. High-sensitivity C-reactive protein: clinical importance. Curr Probl Cardiol 2004; 29: 439-493.
[20] Verma S, Li SH, Badiwala MV, Weisel RD, Fedak PW, Li RK, Dhillon B, Mickle DA. Endothelin antagonism and interleukin-6 inhibition attenuate the proatherogenic effects of C-reactive protein. Circulation 2002; 105: 1890-1896.
[21] Sen U, Moshal KS, Tyagi N, Kartha GK, Tyagi SC. Homocysteine-induced myofibroblast differentiation in mouse aortic endothelial cells. J Cell Physiol 2006; 209: 767-774.