NEURAL REGENERATION RESEARCH
April 2015, Volume 10, Issue 4
www.nrronline.org

RESEARCH ARTICLE

Matrix metalloproteinase 9 level as an indicator for restenosis following cervical and intracranial angioplasty and stenting

Jun-peng Liu, Yin-zhou Wang*, Yong-kun Li, Qiong Cheng, Zheng Zheng

Department of Neurology, Fujian Provincial Hospital, Provincial Clinical Department of Fujian Medical University, Fuzhou, Fujian Province, China

***Correspondence to:**
Yin-zhou Wang, M.D., Ph.D., wphd@163.com.

***doi:**10.4103/1673-5374.155439*
***http:**//www.nrronline.org/*

***Accepted:** 2015-02-09*

Abstract

Cervical and intracranial angioplasty and stenting is an effective and safe method of reducing the risk of ischemic stroke, but it may be affected by in-stent restenosis. The present study investigated serum level of matrix metalloproteinase 9 as a predictor of restenosis after 40 patients underwent cervical and/or intracranial angioplasty and stenting. Results showed that restenosis occurred in 30% (3/10) of patients when the serum level of matrix metalloproteinase 9 at 3 days after surgery was 2.5 times higher than preoperative level. No restenosis occurred when the serum level of matrix metalloproteinase 9 at 3 days after surgery was not 2.5 times higher than preoperative level. Restenosis occurred in 12% (2/17) of patients when the serum level of matrix metalloproteinase 9 was higher than preoperative level for more than 30 days after surgery, but only occurred in 4% (1/23) of patients when the serum level of matrix metalloproteinase 9 was higher than preoperative level for less than 30 days after surgery. However, the differences observed were not statistically significant ($P > 0.05$). Experimental findings indicate that when the serum level of matrix metalloproteinase 9 is 2.5 times higher than preoperative level at 3 days after cervical and intracranial angioplasty and stenting, it may serve as a predictor of in-stent restenosis.

***Key Words:** nerve regeneration; matrix metalloproteinase 9; cervical and intracranial angioplasty and stenting; restenosis; intracranial artery stenosis; neural regeneration*

***Funding:** This study was supported by the Fund for Distinguished Young Doctors from Fujian Provincial Health Department, No. 2011-1-7.*

Liu JP, Wang YZ, Li YK, Cheng Q, Zheng Z (2015) Matrix metalloproteinase 9 level as an indicator for restenosis following cervical and intracranial angioplasty and stenting. Neural Regen Res 10(4):631-635.

Introduction

Ischemic cerebrovascular disease is a disease of high incidence and morbidity in the elderly population all over the world. It is estimated that there are more than 2 million cases of stroke and more than 1.5 million deaths per year in China secondary to ischemic cerebrovascular disease. Among survivors, 66.7% develop disability to varying degrees. Cervical and intracranial angioplasty and stenting is an effective and relatively safe method of reducing the risk of ischemic stroke (Krasniqi et al., 2012; Liu et al., 2013). However, results may be affected by in-stent restenosis (Rutsch et al., 2012; King et al., 2013). Unfortunately, we have no proper indicators to predict and assess the risk of in-stent restenosis and to guide clinical prevention and treatment at present.

Matrix metalloproteinases (MMP) are a family of proteases in which MMP-9 plays an important role in intimal hyperplasia and vascular remodeling (Whatling et al., 2004; Tang et al., 2013; Vandooren et al., 2013; Wu et al., 2013; Zou et al., 2013). A recent study (Rao et al., 2014) has found that MMPs, especially MMP-9, are highly active and expressed at the site of artery in-stent restenosis. MMP-9 promotes smooth muscle cell migration in vessel walls from the media to the intima, proliferating and secreting amounts of extracellular matrix by integrating the degradation and deposition of the extracellular matrix, thereby contributing to artery restenosis (Visse and Nagase, 2003; Silvello et al., 2013; Wang and Cao, 2013; Guo et al., 2014; Yahagi et al., 2014). The formation of artery restenosis is a process of neointimal hyperplasia and vascular remodeling, which is mainly caused by excessive repair after injury. Studies have found that vascular smooth muscle cells do not exist in normal arterial intima. In fact, the rapid degradation of the extracellular matrix around vascular smooth muscle cells is considered to be a prerequisite for their migration (Chaabane et al., 2013). During the degradation of the extracellular matrix, the composition and content of the intima change, which may also influence vascular remodeling when restenosis occurs (Brott et al., 2011).

Neointimal hyperplasia was attenuated and luminal area was reduced in MMP-9 gene knockout mice, which removed the correlation of intimal hyperplasia and vascular remodeling in wild-type mice; while the abilities of migration of vascular smooth muscle cells and collagen contractility declined, indicating that MMP-9 is not only related to matrix

degradation, but also matrix remodeling (Lee et al., 2011). Another study found that MMP-9 activity in peripheral serum was increased and closely related to postoperative restenosis after coronary stent implantation. However, the correlation between serum MMP-9 levels and incidence of in-stent restenosis after cervical and intracranial angioplasty and stenting is poorly understood (Jones et al., 1999).

The present study aims to investigate the relationship between incidence of in-stent restenosis and serum MMP-9 after cervical and intracranial angioplasty and stenting, and provide laboratory evidence for predicting the risk of in-stent restenosis clinically and improving drug treatment for the prevention of in-stent restenosis.

Subjects and Methods

Subjects

Patients with symptomatic or asymptomatic cervical and/or intracranial artery stenosis who underwent cervical and/or intracranial angioplasty and stenting were recruited retrospectively from the neurology clinical database of Fujian Provincial Hospital (Fuzhou, Fujian Province, China). All patients received interventional treatment for the first time. There were 22 males and 18 females, aged from 39 to 75 years of age (average 51 ± 9 years). Among the patients involved, 24 cases had hypertension, 18 had diabetes, 33 had hyperlipidemia, 9 had hyperhomocysteinemia, and 15 were smokers. For all carotid artery stenoses, we used Aviator Plus balloons (Cordis, Roden, the Netherlands) and Precise stents (Cordis, Miami Lakes, FL, USA). For all vertebral, basal and middle cerebral artery stenosis, we used Apollo balloon expansion stents. All stents were placed correctly using the proper size and residual stenosis was less than 20%.

Patients were required to meet the following criteria: (1) Vascular diameter stenosis in patients with intracranial artery stenosis was more than 70%. (2) Vascular diameter stenosis in patients with cervical artery stenosis was more than 50%. (3) Be less than 80-year-old. (4) Patients with acute cerebral infarction (less than 2 weeks) and cerebral hemorrhage, subarachnoid hemorrhage, subdural hemorrhage, epidural hemorrhage were excluded. (5) Patients with leukemia, aplastic anemia, idiopathic thrombocytopenic purpura, or platelets and coagulation dysfunction were excluded. (6) Patients with multiple organ failure were excluded (Fiotti et al., 2006). The control group was 20 healthy adult volunteers recruited from the Health Examination Centre of Fujian Provincial Hospital in China. All details of the study were explained to all subjects, whereupon written informed consent was obtained.

Detection of peripheral MMP-9 and hypersensitive C reactive protein by enzyme linked immunosorbent assay (ELISA)

Serum samples from the median cubital vein of 40 patients and 20 healthy people were collected in Fujian Provincial Hospital and diluted with PBS (pH 7.4). The serum MMP-9 level was analyzed using the ELISA method. In brief, 100 μL serum specimens were applied to the 96-well plates and incubated overnight at 4°C. After three washes with PBS, each well was blocked with 0.5% skimmed milk at room temperature for 1 hour. After another three washes with PBS containing 0.05% Tween 20, mouse anti-human MMP-9 antibody (1:200; Abcam, Cambridge, UK) was applied to wells and incubated at room temperature for 2 hours. Then horseradish peroxidase-conjugated goat anti-mouse IgG (1:1,000; Dako, Glostrup, Denmark) was added, followed by incubation with SureBlue™ TMB Microwell Peroxidase Substrate (KPL, Gaithersburg, MD, USA). After color development, the reaction was stopped with 1 M HCl and the optical density of the solution was read at a wavelength of 450 nm using a microplate reader (iMark™ Microplate Reader; Bio-Rad, Hercules, CA, USA). The serum hypersensitive C reactive protein level was analyzed using an automatic biochemical analyzer (AU5800, BECKMAN, Brea, CA, USA).

Postoperative follow-up

For all subjects, blood samples were taken 0.5 hours before surgery and 1 day, 3 days, 30 days, 6 months and 12 months after surgery to measure the serum levels of MMP-9. Restenosis was observed by carotid and vertebral artery ultrasound or transcranial doppler at 1, 6, 12 months and computer tomography angiography at 6 and 12 months after surgery (data not shown). If restenosis was observed, digital subtraction angiography was taken immediately for measuring the degree of restenosis. Follow-up rate of subjects was higher than 80% and the standard in-stent restenosis extent was greater than 50%. Blood samples were taken only once from the control group as reference.

Statistical analysis

Data are expressed as the mean ± SD. SPSS 13.0 software (SPSS, Chicago, IL, USA) was used to perform statistical analysis. The distribution of continuous variables was assessed and analyzed with one-way analysis of variance and the Fisher protected least significant difference test. A $P < 0.05$ value was considered a significant difference.

Results

Change of serum MMP-9 level after cervical and intracranial angioplasty and stenting

The serum level of MMP-9 showed no significant difference between the experimental group and the normal control group before surgery. However, after surgery, the serum level of MMP-9 was significantly increased and reached a peak at 3 days postoperatively. In more than half the patients, the serum MMP-9 level declined to preoperative level at 30 days after surgery. While in some patients, high level of MMP-9 was observed for more than 1 month after surgery, whereupon levels slowly dropped to preoperative amounts within 6–12 months after surgery (**Figure 1**). The peak of MMP-9 level varied from 1.2 to 3.8 (2.0 ± 0.9) times higher than preoperative levels. To find a better predictor of restenosis after surgery, we divided patients based on the MMP-9 peak level at 3 days after surgery or the duration of high MMP-9 level and analyzed their relationship to the incidence of in-stent

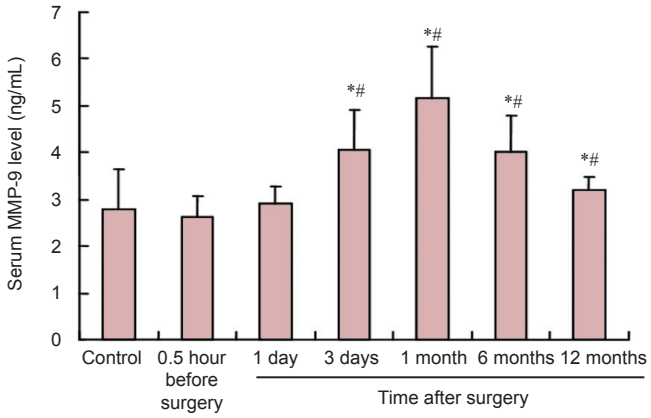

Figure 1 Change of serum matrix metalloproteinase 9 (MMP-9) level in patients after cervical and intracranial angioplasty and stenting.
Data are expressed as the mean ± SD (n = 40). The distribution of continuous variables was assessed and analyzed with one-way analysis of variance with the Fisher protected least significant difference test. *P < 0.05, *vs.* control group; #P < 0.05, *vs.* 0.5 hour before surgery.

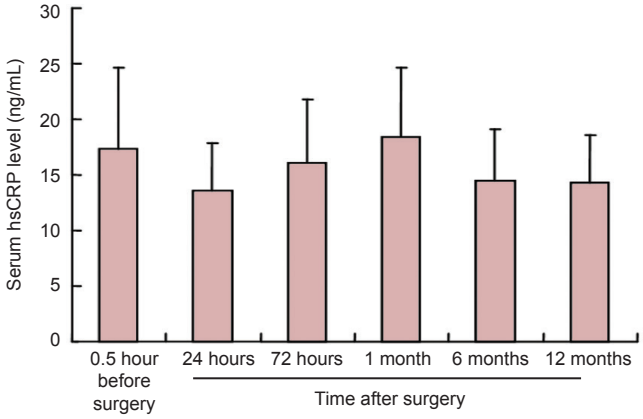

Figure 2 Change of serum hypersensitive C reactive protein (hsCRP) level after cervical and intracranial angioplasty and stenting.
Data are expressed as the mean ± SD (n = 40). The distribution of continuous variables was assessed and analyzed with one-way analysis of variance with the Fisher protected least significant difference test.

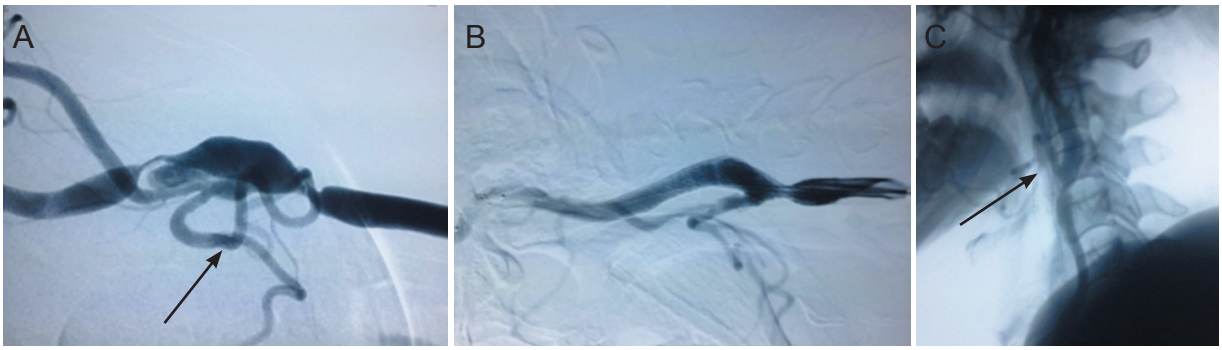

Figure 3 Subtracted angiography of a male 65-year-old patient with severe stenosis in the left internal carotid artery.
(A) 0.5 hour before surgery; (B) 0.5 hour after angioplasty and stenting; (C) unsubtracted angiography of the same artery 1 year after interventional surgery. Arrows refer to the stenosis.

restenosis. There were 10 patients in whom the serum level of MMP-9 was 2.5 times higher than preoperative level at 3 days after surgery (high peak level group), and 30 patients in whom the peak level of serum MMP-9 was not 2.5 times higher than preoperative level at 3 days after surgery (low peak level group). By contrast, 17 patients displayed a serum level of MMP-9 at 30 days still higher than preoperative level (long duration group), and 23 patients in whom the serum level of MMP-9 at 30 days was declined to preoperative level (short duration group).

Change of serum hypersensitive C reactive protein level after cervical and intracranial angioplasty and stenting

The serum level of hypersensitive C reactive protein before and after surgery was similar, but was slightly higher than that in the control group (data not shown). However, there was no significant difference (P > 0.05). After surgery, the level of hypersensitive C reactive protein increased and decreased at different time points, but there was no clear trend related to the operation (**Figure 2**). The level of hypersensitive C reactive protein showed no significant difference among patients who had different MMP-9 levels. Therefore, this study demonstrates that hypersensitive C reactive protein does not have any potential to predict prognosis following surgery.

Follow-up results after cervical and/or intracranial angioplasty and stenting

Follow-up lasted for 18 months and three patients were confirmed to have in-stent restenosis (**Figure 3**). The three patients belonged to the MMP-9 high peak level group (n = 10 patients), while no in-stent restenosis was observed in the MMP-9 low peak level group (n = 30 patients). There were significant differences in the incidence of in-stent restenosis between these two groups (30% *vs.* 0, P < 0.01). Two patients with in-stent restenosis belonged to the MMP-9 long duration group (n = 17 patients), and one patient with in-stent restenosis belonged to the MMP-9 short duration group (n = 23 patients). Unfortunately, the incidence of in-stent restenosis between these two groups was not statistically significant (12% *vs.* 4%, P > 0.05).

Discussion

Endovascular stenting has become one of the main treat-

ment methods of cervical and intracranial artery stenosis due to satisfactory clinical efficacy, but results may be affected by in-stent restenosis (Hou et al., 2014; Li et al., 2014; Sun et al., 2014). Symptomatic intracranial atherosclerotic stenosis can be cured by implanting Wingspan stents (McTaggart et al., 2014). Krasniqi et al. (2012) showed that the restenosis rate of carotid artery stenting was 4.3% at a mean follow-up time of 22 months. Previous studies into symptomatic vertebral artery and intracranial atherosclerotic lesion stenting showed that the rate of restenosis was 32% in 6 months after bare stent implantation (Saatci Yaşar et al., 2009). But over the past few years, carotid endovascular techniques have been markedly refined with the availability of wires and stents that are specifically designed for the carotid artery and it is likely that these modifications will improve efficacy and reduce the risks associated with treatment in the future.

It has been reported that the level of MMP-9 significantly increased after atherosclerosis. Previous studies performed in mice, rats, and rabbits have also demonstrated that arterial injury is a potent activator of the MMP system (Bendeck et al., 1994; Zempo et al., 1994; Strauss et al., 1996; Webb et al., 1997; Aikawa et al., 1998; Bassiouny et al., 1998; Jenkins et al., 1998; Lijnen et al., 1998). Feldman et al. (2001) provided evidence that MMP activation occurred after stenting, and activation of latent MMP-9 was found in stented arteries. MMP-9 is the main MMP that vascular wall cells secreted, and it plays an important role in neointimal hyperplasia and vascular remodeling (Liu et al., 2009). MMP-9 promotes migration of vessel wall smooth muscle cells from the media to the intima, and also enables proliferation and secretion of the extracellular matrix by integrating its degradation and deposition, thereby contributing to artery restenosis. The formation of artery restenosis is a process of neointimal hyperplasia and vascular remodeling, which is mainly caused by excessive repair after injury. Studies have found that vascular smooth muscle cells do not exist in normal arterial intima, and the rapid degradation of the extracellular matrix of vascular smooth muscle cells is considered to be a prerequisite for their migration. The degradation of the extracellular matrix relates not only to the proliferation and migration of vascular smooth muscle cells, but also to the changes in the composition and content of the arterial intima (Brott et al., 2011).

Intimal hyperplasia and luminal area is reduced in MMP-9 gene deficient mice, which eliminated the correlation of wild-type endometrial hyperplasia and geometric remodeling. Furthermore, migration of vascular smooth muscle cells and collagen contractility declined, indicating that MMP-9 was not only related to matrix degradation, but also matrix remodeling (Lee et al., 2011). Bendeck et al. (2002) found that serum MMP-9 in mice was expressed from the first day after injury of the carotid artery and reached a peak at 6 days. MMP-9 levels then subsequently decreased gradually. Other animal experiments also confirmed that the expression of MMP-9 increased significantly in a time-dependent manner after stent implantation (Hou et al., 2002). Jones et al. (1999) found that MMP-9 activity in the serum increased and was closely related to postoperative restenosis after coronary stent implantation. Other studies also have shown that MMP-9 participated in repair after arterial injury and restenosis. The present study followed patients who underwent cervical and intracranial angioplasty and stenting for 18 months and found that when the level of serum MMP-9 was 2.5 times higher than normal levels at 3 days after surgery, the rate of restenosis was 30%, which showed a high relationship with, and had an important value in predicting, restenosis after cervical and intracranial angioplasty and stenting. Therefore, this study showed that when the level of serum MMP-9 is 2.5 times higher than normal levels at 3 days after surgery, it may be a new indicator for predicting restenosis after implantation of a stent. Since in-stent restenosis is one of the most important factors that affect the outcomes of angioplasty and stenting, our findings help us to determine the high risk patients who are at risk of developing in-stent restenosis allowing intensified medical treatment to be given to reduce this complication. It has been reported recently that hypersensitive C reactive protein plays a direct role in the process of atherosclerosis and vascular injury. In our study, we also examined the perioperative level of serum hypersensitive C reactive protein, a common inflammatory indicator. We did not find that hypersensitive C reactive protein had any predictive value for in-stent restenosis.

Although the predictive value of MMP-9 was highly significant, this study was not powered for calculation of clinical cutoff values due to the relatively low number of patients who develop in-stent restenosis after angioplasty and stenting. These findings, therefore, need to be further evaluated in a larger, multi-center and multi-factor analysis trial. The present results indicate a new way to predict in-stent restenosis after angioplasty and stenting, thus guiding drug therapy after interventional treatment of artery stenosis.

Acknowledgments: *We would like to thank Mr. Tao Zhang from the Second Hospital of Fuzhou Affiliated to Xiamen University in China for his assistance with data collection.*

Author contributions: *JPL was responsible for the concept and design of the study, analyzing experimental data, writing the paper, and performing statistical analysis. JPL was also in charge of the funds. YZW supervised the study and revised the article. YKL, QC and ZZ provided the data and technical information. All authors approved the final version of the paper.*

Conflicts of interest: *None declared.*

References

Aikawa M, Rabkin E, Okada Y, Voglic SJ, Clinton SK, Brinckerhoff CE, Sukhova GK, Libby P (1998) Lipid lowering by diet reduces matrix metalloproteinase activity and increases collagen content of rabbit atheroma: a potential mechanism of lesion stabilization. Circulation 97:2433-2444.

Bassiouny HS, Song RH, Hong XF, Singh A, Kocharyan H, Glagov S (1998) Flow regulation of 72-kD collagenase IV (MMP-2) after experimental arterial injury. Circulation 98:157-163.

Bendeck MP, Zempo N, Clowes AW, Galardy RE, Reidy MA (1994) Smooth muscle cell migration and matrix metalloproteinase expression after arterial injury in the rat. Circ Res 75:539-545.

Bendeck MP, Conte M, Zhang M, Nili N, Strauss BH, Farwell SM (2002) Doxycycline modulates smooth muscle cell growth, migration, and matrix remodeling after arterial injury. Am J Pathol 160:1089-1095.

Brott TG, Halperin JL, Abbara S, Bacharach JM, Barr JD, Bush RL, Cates CU, Creager MA, Fowler SB, Friday G, Hertzberg VS, McIff EB, Moore WS, Panagos PD, Riles TS, Rosenwasser RH, Taylor AJ (2011) 2011 ASA/ACCF/AHA/AANN/AANS/ACR/ASNR/CNS/SAIP/SCAI/SIR/SNIS/SVM/SVS Guideline on the Management of Patients With Extracranial Carotid and Vertebral Artery Disease: Executive Summary: A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, and the American Stroke Association, American Association of Neuroscience Nurses, American Association of Neurological Surgeons, American College of Radiology, American Society of Neuroradiology, Congress of Neurological Surgeons, Society of Atherosclerosis Imaging and Prevention, Society for Cardiovascular Angiography and Interventions, Society of Interventional Radiology, Society of NeuroInterventional Surgery, Society for Vascular Medicine, and Society for Vascular Surgery Developed in Collaboration With the American Academy of Neurology and Society of Cardiovascular Computed Tomography. J Am Coll Cardiol 57:1002-1044.

Chaabane C, Otsuka F, Virmani R, Bochaton-Piallat ML (2013) Biological responses in stented arteries. Cardiovasc Res. 2013 Jul 15;99(2):353-63.

Feldman LJ, Mazighi M, Scheuble A, Deux JF, De Benedetti E, Badier-Commander C, Brambilla E, Henin D, Steg PG, Jacob MP (2001) Differential expression of matrix metalloproteinases after stent implantation and balloon angioplasty in the hypercholesterolemic rabbit. Circulation 103:3117-3122.

Fiotti N, Altamura N, Fisicaro M, Carraro N, Uxa L, Grassi G, Torelli L, Gobbato R, Guarnieri G, Baxter BT, Giansante C (2006) MMP-9 microsatellite polymorphism and susceptibility to carotid arteries atherosclerosis. Arterioscler Thromb Vasc Biol 26:1330-1336.

Guo L, Ning W, Tan Z, Gong Z, Li X (2014) Mechanism of matrix metalloproteinase axis-induced neointimal growth. J Mol Cell Cardiol 66:116-125.

Hou G, Vogel WF, Bendeck MP (2002) Tyrosine kinase activity of discoidin domain receptor 1 is necessary for smooth muscle cell migration and matrix metalloproteinase expression. Circ Res 90:1147-1149.

Hou Y, Ding SF, Wang HJ, Jiang JQ, Fu WB, Wang H, Chen ZN (2014) Variation in serum visfatin levels 24 hours after coronary stent implantation. Zhongguo Zuzhi Gongcheng Yanjiu 18:2619-2624.

Jenkins GM, Crow MT, Bilato C, Gluzband Y, Ryu WS, Li Z, Stetler-Stevenson W, Nater C, Froehlich JP, Lakatta EG, Cheng L (1998) Increased expression of membrane-type matrix metalloproteinase and preferential localization of matrix metalloproteinase-2 to the neointima of balloon-injured rat carotid arteries. Circulation 97:82-90.

Jones JL, Glynn P, Walker RA (1999) Expression of MMP-2 and MMP-9, their inhibitors, and the activator MT1-MMP in primary breast carcinomas. J Pathol 189:161-168.

King L, Byrne RA, Mehilli J, Schömig A, Kastrati A, Pache J (2013) Five-year clinical outcomes of a polymer-free sirolimus-eluting stent versus a permanent polymer paclitaxel-eluting stent: final results of the intracoronary stenting and angiographic restenosis - test equivalence between two drug-eluting stents (ISAR-TEST) trial. Catheter Cardiovasc Interv 81:E23-E28.

Krasniqi N, Turgut M, Husmann M, Roffi M, Schwarz U, Greutmann M, Lüscher TF, Amann B, Corti R (2012) Carotid artery stenting: a single center "real world" experience. PLoS One 7:e35300.

Lee SY, Hörbelt M, Mang HE, Knipe NL, Bacallao RL, Sado Y, Sutton TA (2011) MMP-9 gene deletion mitigates microvascular loss in a model of ischemic acute kidney injury. Am J Physiol Renal Physiol 301:F101-109.

Li LF, Liu HY, Zhao XH (2014) Application situation of degradable coronary stents. Zhongguo Zuzhi Gongcheng Yanjiu 18:1270-1276.

Lijnen HR, Van Hoef B, Lupu F, Moons L, Carmeliet P, Collen D (1998) Function of the plasminogen/plasmin and matrix metalloproteinase systems after vascular injury in mice with targeted inactivation of fibrinolytic system genes. Arterioscler Thromb Vasc Biol 18:1035-1045.

Liu G, Wang B, Zhang J, Jiang H, Liu F (2009) Total panax notoginsenosides prevent atherosclerosis in apolipoprotein E-knockout mice: Role of downregulation of CD40 and MMP-9 expression. J Ethnopharmacol 126:350-354.

Liu J, Yao GE, Zhou HD, Jiang XJ, Chen Q (2013) Prevention of hemodynamic instability in extra-cranial carotid angioplasty and stenting using temporary transvenous cardiac pacemaker. Cell Biochem Biophys 65:275-279.

McTaggart RA, Marks MP (2014) The case for angioplasty in patients with symptomatic intracranial atherosclerosis. Front Neurol. 2014 Apr 11;5:36.

Rao VH, Kansal V, Stoupa S, Agrawal DK (2014) MMP-1 and MMP-9 regulate epidermal growth factor-dependent collagen loss in human carotid plaque smooth muscle cells. Physiol Rep 2:e00224.

Rutsch W, Scheller B, Borges AC, Bräutigam M, Clever Y, Cremers B, Dietz U, Richter W, Speck U (2012) Intracoronary local paclitaxel delivery by X-ray contrast media for in-stent restenosis: a clinical pilot study to assess safety and tolerability. Minerva Cardioangiol 60:415-423.

Saatci Yaşar A, Bilen E, Bilge M, Tolunay H, Ipek G (2009) Development of atherosclerosis and in-stent restenosis in an unusual case of dual left anterior descending coronary artery. Anadolu Kardiyol Derg 9:E1.

Silvello D, Narvaes LB, Albuquerque LC, Forgiarini LF, Meurer L, Martinelli NC, Andrades ME, Clausell N, Santos KGd, Rohde LE (2013) Serum levels and polymorphisms of matrix metalloproteinases (MMPs) in carotid artery atherosclerosis: higher MMP-9 levels are associated with plaque vulnerability. Biomarkers 19:49-55.

Strauss BH, Robinson R, Batchelor WB, Chisholm RJ, Ravi G, Natarajan MK, Logan RA, Mehta SR, Levy DE, Ezrin AM, Keeley FW (1996) In vivo collagen turnover following experimental balloon angioplasty injury and the role of matrix metalloproteinases. Circ Res 79:541-550.

Sun H, Yan YS, Chen QQ, Li SB (2014) Fibroin in small-caliber vascular prostheses. Zhongguo Zuzhi Gongcheng Yanjiu 18:2576-2581.

Tang J, Chen T, Mi J, Xu AG, Wang YD, Zhang J, Qi XQ (2013) Effect of bone marrow mononuclear cell transplantation on angiogenesis and expression of cytokines following myocardial infarction. Zhongguo Zuzhi Gongcheng Yanjiu 17:5840-5846.

Vandooren J, Van den Steen PE, Opdenakker G (2013) Biochemistry and molecular biology of gelatinase B or matrix metalloproteinase-9 (MMP-9): The next decade. Crit Rev Biochem Mol 48:222-272.

Visse R, Nagase H (2003) Matrix metalloproteinases and tissue inhibitors of metalloproteinases: structure, function, and biochemistry. Circ Res 92:827-839.

Wang M, Cao BZ (2013) Glial cell responses and matrix metalloproteinase-9 expression in the brain of chronic vascular dementia rat models. Zhongguo Zuzhi Gongcheng Yanjiu 17:1212-1219.

Webb KE, Henney AM, Anglin S, Humphries SE, McEwan JR (1997) Expression of matrix metalloproteinases and their inhibitor TIMP-1 in the rat carotid artery after balloon injury. Arterioscler Thromb Vasc Biol 17:1837-1844.

Whatling C, McPheat W, Hurt-Camejo E (2004) Matrix management: assigning different roles for MMP-2 and MMP-9 in vascular remodeling. Arterioscler Thromb Vasc Biol 24:10-11.

Wu HD, Bai X, Chen DM, Cao HY, Qin L (2013) Association of genetic polymorphisms in matrix metalloproteinase-9 and coronary artery disease in the Chinese Han population: a case-control study. Genet Test Mol Biomarkers 17:707-712.

Yahagi K, Otsuka F, Sakakura K, Sanchez OD, Kutys R, Ladich E, Kolodgie FD, Virmani R, Joner M (2014) Pathophysiology of superficial femoral artery in-stent restenosis. J Cardiovasc Surg (Torino) 55:307-323.

Zempo N, Kenagy RD, Au YPT, Bendeck M, Clowes MM, Reidy MA, Clowes AW (1994) Matrix metalloproteinases of vascular wall cells are increased in balloon-injured rat carotid artery. J Vasc Surg 20:209-217.

Zou Y, Fu Y, Davies MG (2013) Gα_q G proteins modulate MMP-9 gelatinase during remodeling of the murine femoral artery. J Surg Res 181:32-40.

Copyedited by Aprico K, Norman C, Yu J, Yang Y, Li CH, Song LP, Zhao M