CASE REPORT
Korean Circulation J 2005;35:860-863
ISSN 1738-5520


# Successful Management of a Patient with Factor XI Deficiency and Unstable Angina by Percutaneous Coronary Intervention

Sang Hyun Lee, MD, Myung Ho Jeong, MD, Il Seok Sohn, MD, Sang Yup Lim, MD,
Seo Na Hong, MD, Dong Goo Kang, MD, Kye Hun Kim, MD, Hyung Wook Park, MD,
Young Joon Hong, MD, Ju Han Kim, MD, Weon Kim, MD, Young Keun Ahn, MD,
Jeong Gwan Cho, MD, Jong Chun Park, MD and Jung Chaee Kang, MD

*The Heart Center of Chonnam National University Hospital, Chonnam National University Research Institute of Medical Sciences, Gwangju, Korea*

**ABSTRACT**

Factor XI deficiency is a very rare congenital coagulation disorder. Bleeding complications should be considered when treating a patient with unstable angina and congenital coagulation disorder during and after percutaneous coronary intervention (PCI). Thrombotic complications can develop after fresh frozen plasma (FFP) transfusion and drug-eluting stent (DES) implantation. We report here on the successful management of a patient having unstable angina with factor XI deficiency, and this patient was treated with PCI under intravascular guidance and with the aid of FFP and hemostatic devices. **(Korean Circulation J 2005;35:860-863)**

**KEY WORDS :** Factor XI deficiency ; Angioplasty.

## Introduction

Factor XI (FXI) is a plasma glycoprotein that participates in the early phase of the intrinsic pathway for secondary hemostasis and it is essential for normal hemostasis. Factor XI deficiency is also called hemophilia C. A particularly high frequency of factor XI deficiency has been reported in Ashkenazi Jews, but this disease is very rare in other ethnic groups. The incidence in the general population is one in a million persons.[1)2)]

Until now there is no uniform guideline for dealing with FXI deficiency during percutaneous coronary intervention (PCI). The thrombotic risk may be increased during and after PCI, and especially after fresh frozen plasma (FFP) transfusion and drug-eluting stent (DES) implantation. We report here on the successful management of a patient who had severe FXI deficiency and unstable angina, and this patient underwent PCI without incurring any bleeding or thrombotic complications.

**Received** : May 25, 2005
**Accepted** : July 27, 2005
**Correspondence** : Myung Ho Jeong, MD, The Heart Center of Chonnam National University Hospital, Chonnam National University Research Institute of Medical Sciences, 8 Hak-dong, Dong-gu, Gwangju 501-757, Korea
Tel: 82-62-220-6243, Fax: 82-62-228-7174
E-mail: myungho@chollian.net

## Case

A 52 year-old male patient presented with new onset chest pain that had been increasing for the previous two weeks. His chest pain was "squeezing" in nature and it radiated to the left neck and shoulder; the frequency of chest pain had recently increased and it was now precipitated by minor exertion. He was a 45 pack-year current smoker.

One year before the occurrence of his angina pectoris, he was diagnosed as having severe factor XI deficiency during a pre-operative evaluation for his internal hemorrhoids. The activated partial thromboplastin time (aPTT) was above 100 seconds (normal: 26.4-41 sec). The level of factor XI was markedly decreased to 1.7 U/dL (normal: 70-150 U/dL), and the other factors' levels were within their normal range. Neither he nor his family members had any bleeding tendency.

On admission, the resting ECG showed T wave inversion over the precordial leads (Fig. 1). The left ventricular ejection fraction, as determined by echocardiogram, was 63% and any regional wall motion abnormality was not noted. The laboratory data, including the lipid profiles and cardiac enzymes, were within the normal range, except for the aPTT.

A loading dose of 300 mg aspirin and 300 mg clopidogrel were given and this was followed by 100 mg

aspirin and 75 mg clopidogrel daily. On the third day, a diagnostic coronary angiogram (CAG) was done. Before the femoral puncture, 400 mL of FFP was transfused (half dose of 15 mL/kg). The activated clotting time (ACT) measured at the cardiac catheterization laboratory was 230 seconds. Left femoral puncture was done with a Seldinger needle, and after the insertion of a 7F sheath and confirmation that the puncture site was absolutely clear of oozing, 2500 units of low molecular weight heparin (LMWH) were injected. CAG revealed a critical stenosis in the middle left anterior descending artery (LAD) with TIMI II flow and a focal stenosis was seen in the first diagonal branch. An additional 5,000 units of LMWH were administered and after pre-dilation with a 2.5 mm balloon, intravascular ultrasound (IVUS) performed. This showed huge calcified plaques around the target lesion with the lesion length being 25 mm. A 3.5×32 mm paclitaxel-eluting

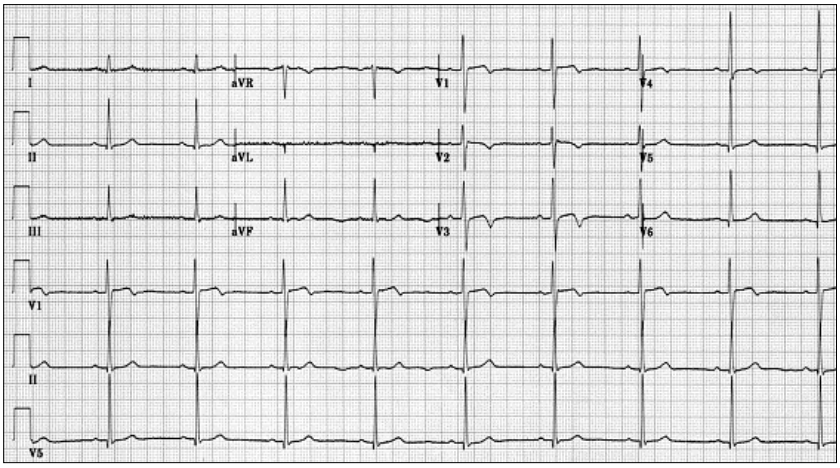


**Fig. 1.** Electrocardiogram showed the ST segment and T wave change over V1-4.

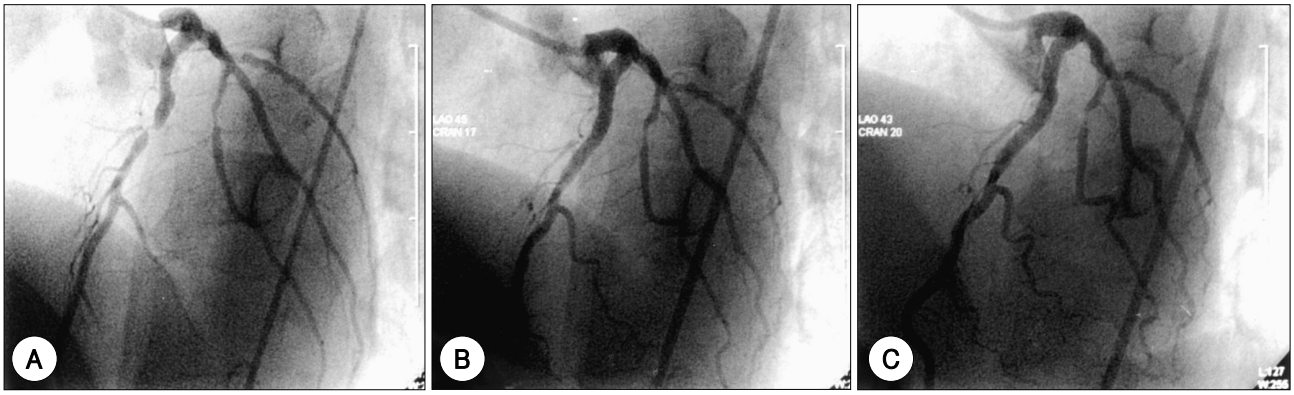


**Fig. 2.** A diagnostic coronary angiogram of the left coronary artery at the anterior oblique view showed a critical stenosis in the middle left anterior descending artery (LAD)(A). A drug-eluting stent (3.5×32 mm, Taxus® stent) was successfully deployed in the middle LAD (B). The six-month follow-up coronary angiogram showed no restenosis in the previously stented site (C).

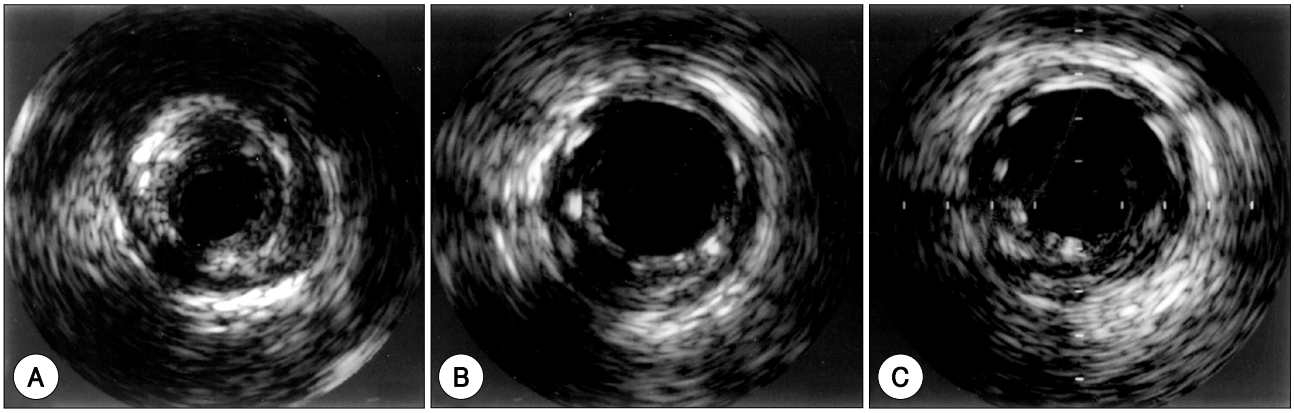


**Fig. 3.** Intravascular ultrasound (IVUS) revealed huge calcified plaques in the middle left anterior descending artery (LAD)(A). Immediately after placing a drug-eluting stent, the stent expanded very well in the middle LAD on the IVUS examination (B). No neointimal hyperplasia was shown on the six-month follow-up IVUS (C).

(Taxus®) stent was deployed in the middle LAD. The final CAG and IVUS showed no residual stenosis and good apposition of the stent against the vessel wall (Fig 2, 3). The post-procedural ACT was prolonged up to 410 seconds. A percutaneous closing device, Angioseal™ (St. Jude Medical), was employed for the closure of the femoral arterial puncture site and an additional 400 mL (the last half dose of 15 mL/kg) FFP was then transfused. The aPTT was corrected to 51 seconds after transfusion, and no puncture site bleeding or hematoma developed. The patient had an uneventful recovery after discharge. Combined oral antiplatelet agents, 100 mg aspirin and 75 mg clopidogrel, were administered during the 6-month clinical follow-up.

A follow-up CAG was done at six months after the PCI. On admission, the aPTT was prolonged up to 123 seconds. Two hours before the follow-up CAG, 400 mL FFP was transfused. After the right femoral puncture, the ACT was 101 seconds and 2500 units of LMWH were also injected. Neither in-stent restenosis nor de novo lesion was observed on the follow-up CAG. The follow-up intravascular ultrasound (IVUS) examination revealed no neointimal hyperplasia (Fig. 2, 3) in the previous stented LAD. For homeostasis, another percutaneous closing device, Perclose® (Abbott), was used and 400 mL FFP was also transfused. After this procedure, the aPTT was 57 seconds and the patient had an uneventful clinical course during the two-month clinical follow-up after his discharge.

## Discussion

Performing PCI in the patients suffering with coagulation disorders requires very careful management of the bleeding complications and thrombotic events after FFP transfusion and DES placement, as compared with average patients. In this case report, the patient underwent successful PCI with the aid of a percutaneous closure device and the implantation of a IVUS guided DES.

Factor XI (FXI) deficiency is inherited as an autosomal recessive trait.[3] 53 mutations have been reported so far in the ethic populations of Ashkenazi Jews and Iraqi Jews, the English population and the Basque people of southwest France. The mutant alleles of the Ashkenazi Jews are known to be as high as 8.8% of their population. There are four types of mutations in Jewish people, but mutations have also been reported in non-Jewish people. For Koreans, there were only few case reports on children having Factor XI deficiency.[4][5] The incidence of this disorder in the general population is one in one million people.[1]

The gene encoding FXI is located on the distal arm of chromosome 4 (4q35). FXI is synthesized in the liver and it has a half-life of about 52 hours. In the homozygous form of FXI deficiency, the aPTT is prolonged; the plama level of FXI under 15 U/dL is considered as severe FXI deficiency and below the level of 70 U/dL is considered as mild deficiency.[3] Factor XI (FXI) deficiency is called hemophilia C. Unlike hemophilia A or B, the people with hemophilia C do not bleed spontaneously.[2] The clinical manifestations of FXI deficiency are variable and bleeding occurs only after trauma or surgical procedures.[3] The prevention of bleeding is somewhat different for hemophilia C. FFP is the treatment of choice for the patient with severe FXI deficiency who are undergoing surgery. FXI concentrates can be used, but this treatment may induce thrombosis in approximately 10% of the patients. Transfusion of FXI concentrates does not cause volume overload, particularly in those patients suffering with cardiovascular disease.[2] There are some reports that recombinant FVIIa has successfully prevented bleeding during or after surgery in those patient with FXI inhibitors. FXI inhibitors can develop in the patients who have a FXI level<1 U/dL and who are exposed to plasma. The lack of correction of a prolonged aPTT with administering normal plasma should arouse the clinical suspicion of the presence of inhibitor.[6][7] Replacement therapy usually consists of FFP with a target level of 30-40 U/dL to achieve the treatment goal, and the FFP should be started with an infusion of 15 mL/kg/day for maintaining the FXI level for 7 days.[2] The patients with severe FXI deficiency who need to undergo surgical procedures will require prophylactic treatment, even if they have a negative history of excessive bleeding.[3] It is recommended to administer FFP to these patients with severe FXI two hours before surgery.[8]

Hemophilia A or B is known to provide protection against myocardial infarction, even though severe FXI deficiency does not have a protective effect for myocardial infarction.[9]

Because of the lack of experience with PCI in those patients with factor deficiency, there are still no uniform guidelines for treating hemophilia during PCI. There are only a few reports on the successful management of these patients without bleeding complications during PCI procedures and cardiac surgery.[10][11]

In this case, the patient had a severe deficiency of factor XI with a level of 1.7 U/dL and this was somewhat corrected after the transfusion of FFP. The use of antiplatelet agents before, during and after such a procedure should be considered. Because of the differences between primary and secondary hemostasis, these patient could be prescribed aspirin and clopidogrel. Salomon[3] insisted that the patients having a risk for atherosclerosis can be treated with anti-platelet agents like aspirin or clopidogrel, and the patient suffering with atrial fi-

brillation can be treated safely with warfarinXXX under 2.5 of the international normalization ratio (INR).

We suggest that during PCI after FFP administration, the ACT should be closely monitored for unwanted thrombogenesis or bleeding complications; for the ideal level of ACT, heparin or LMWH can be used safely with ACT monitoring. Daltheparin can be safely used in acute coronary syndrome.[12]

Arteriotomy closure devices (ACD) are now being used as an alternative method for manual compression after PCI procedures. The Angioseal™ (St. Jude Medical) hemostatic closure device is composed of an absorbable collagen sponge and an absorbable polymer anchor that are connected by an absorbable self-tightening suture. Hemostasis is primarily achieved by the mechanical means of the anchor-arteriotomy sandwich. The Perclose® (Abbott) is a percutaneous arterial suture device that is used for direct tying of the vessel wall. The meta-analysis of ACDs that included the Angioseal™ and Perclose® reported that the risk of incurring access-site complications was similar between the ACDs and mechanical compression.[13][14] Jessup et al.[15] and Boccalandro et al.[16] insisted that Angioseal™ and Perclose® could be safely used for those patients treated with warfarin and abciximab during both emergency and elective PCI procedures. Patients who underwent Angioseal™ could walk and they were discharged earlier than those patients who underwent manual compression.[17]

In our experience, Angioseal™ and Perclose® could be safely used for achieving hemostasis with FFP after PCI in the patient with severe FXI deficiency. However, another report showed that FFP may not be required even for the patient severe factor XI deficiency, if hemostasis was completely acquired during and after the procedure.[18]

Bleeding control is the main issue for performing a surgical operation on the patients of FXI deficiency. But for PCI, both prevention of bleeding and thrombogenesis during the procedure should be considered. Thus, we transfused a half dose of FFP before the arterial procedure and an injection of heparin with close monitoring of the ACT during procedure; for the complete hemostasis of the arterial access site, Angioseal™ and Perclose® device were used with FFP. PCI with IVUS-guided DES implantation was successfully performed without incurring acute or subacute stent thrombosis. Combined anti-platelet medications, aspirin and clopidogrel, were administered during the 6-month clinical follow-up.

## REFERENCES


1) O'Connell NM. *Factor XI deficiency from molecular genetics to clinical management. Blood Coagul Fibrinolysis 2003;14 (Suppl 1):S59-64.*
2) Bolton-Maggs PH. *Factor XI deficiency and its management. Haemophilia 2000;6 (Suppl 1):100-9.*
3) Salomon O, Seligsohn U. *New observations on factor XI deficiency. Haemophilia 2004;10 (Suppl 4):184-7.*
4) Rha JY, Kook JH, Kook H, et al. *Three cases of factor XI deficiency. Korean J Pediatr Hematol-Oncol 2001;8:344-8.*
5) Cho YK, Lim JY, Jung YS, et al. *Two cases of factor XI deficiency in sisters. J Korean Pediatr Soc 1998;41:401-4.*
6) Bern MM, Sahud M, Zhukov O, Qu K, Mitchell W Jr. *Treatment of factor XI inhibitor using recombinant activated factor VIIa. Haemophilia 2005;11:20-5.*
7) Lawler P, White B, Pye S, et al. *Successful use of recombinant factor VIIa in a patient with inhibitor secondary to severe factor XI deficiency. Haemophilia 2002;8:145-8.*
8) Borud LJ, Matarasso A, Spaccavento CM, Hanzlik RM. *Factor XI deficiency: implications for management of patients undergoing aesthetic surgery. Plast Reconstr Surg 1999;104:1907-13.*
9) Salomon O, Steinberg DM, Dardik R, et al. *Inherited factor XI deficiency confers no protection against acute myocardial infarction. J Thromb Haemost 2003;1:658-61.*
10) Arora UK, Dhir M, Cintron G, Strom JA. *Successful multi-vessel PCI with bivalirudin in a patient with severe hemophilia A: a case report and review of literature. J Invasive Cardiol 2004;16:330-2.*
11) MacKinlay N, Taper J, Renisson F, Rickard K. *Cardiac surgery and catheterization in patients with haemophilia. Haemophilia 2000;6:84-8.*
12) Kim JH, Jeong MH. *Is daltheparin safe in acute coronary syndrome? Korean Circ J 2003;33:653-5.*
13) Koreny M, Riedmuller E, Nikfardjam M, Siostrzonek P, Mullner M. *Arterial puncture closing devices compared with standard manual compression after cardiac catheterization: systematic review and meta-analysis. JAMA 2004;291:350-7.*
14) Nikolsky E, Mehran R, Halkin A, et al. *Vascular complications associated with arteriotomy closure devices in patients undergoing percutaneous coronary procedures: a meta-analysis. J Am Coll Cardiol 2004;44:1200-9.*
15) Jessup DB, Coletti AT, Muhlestein JB, Barry WH, Shean FC, Whisenant BK. *Elective coronary angiography and percutaneous coronary intervention during uninterrupted warfarin therapy. Catheter Cardiovasc Interv 2003;60:180-4.*
16) Boccalandro F, Assali A, Fujise K, Smalling RW, Sdringola S. *Vascular access site complications with the use of closure devices in patients treated with platelet glycoprotein IIb/IIIa inhibitors during rescue angioplasty. Catheter Cardiovasc Interv 2004;63:284-9.*
17) Seok JH, Park YH, Kim MK, et al. *Efficacy and complications of Angio-Seal® device in patient undergoing coronary angiography and angioplasty. Korean Circ J 2003;33:574-82.*
18) Salomon O, Steinberg DM, Tamarin I, Zivelin A, Seligsohn U. *Plasma replacement therapy during labor is not mandatory for women with severe factor XI deficiency. Blood Coagul Fibrinolysis 2005;16:37-41.*