Aging, Hypercoagulability, and Leg Necrosis in Critical Limb Ischemia

Jong Kwon Park,[1] Dong Sik Bae,[1] Yong Han Kim,[2] and Kyong Jin Shin,[3] Busan, Republic of Korea

Background: Aging is associated with changes in coagulation status and progression of arterial insufficiency. The purpose of this study was to identify interrelationships among aging, coagulation status, and leg necrosis in patients with critical limb ischemia (CLI).
Methods: Between March 2010 and February 2013, 103 consecutive patients with CLI were enrolled in this study. Retrospective analyses were performed on patient characteristics including age, gender, the presence or the absence of leg necrosis, diabetes mellitus (DM), hypertension, and smoking, and preoperatively measured baseline coagulability factors, which included measurements of coagulation factors anticardiolipin antibodies IgG and IgM, lupus anticoagulant and factor 8, the fibrinolytic factor tissue plasminogen activator (t-PA), and natural anticoagulants proteins C and S and antithrombin III.
Results: Among 103 patients with CLI, a total of 49 legs from 41 patients presented varying degrees of necrosis. CLI patients with DM and hypertension showed significantly increased incidences of leg necrosis compared with those without ($P = 0.000$, 0.039, respectively). Patients with CLI and leg necrosis were significantly older compared with the age of those without necrosis ($P = 0.007$). Blood levels of anticardiolipin antibodies IgG and IgM, factor 8, lupus anticoagulant, and t-PA tended to increase with age. However, blood levels of proteins C and S and antithrombin III decreased with patient age. Patients with CLI and leg necrosis showed significantly increased levels of lupus anticoagulant ($P = 0.049$) and significantly decreased levels of proteins C and S ($P = 0.009$ and 0.018, respectively) compared with patients without leg necrosis.
Conclusions: Patients with CLI and leg necrosis were significantly older compared with those without necrosis; similarly, our results revealed age-related hypercoagulability, with significantly elevated coagulation factor lupus anticoagulant and decreased natural anticoagulants protein C and S levels. From these observations, we conclude that age-related hypercoagulability may be an important mechanism that may facilitate leg necrosis in patients with CLI.

INTRODUCTION

Critical limb ischemia (CLI) is defined for all patients with chronic ischemic rest pain, ulcers, or gangrene attributable to objectively proven arterial occlusive disease.[1] CLI corresponds to Fontaine stages III and IV or Rutherford categories 4, 5, or 6.[2] Aging is an important factor that predisposes patients with peripheral arterial disease to ischemic leg necrosis.[3,4] In normal healthy individuals, it has been shown that blood levels of coagulation factors and natural anticoagulants, such as factor VIII, protein C, protein S, and antithrombin III, change with age and increasing blood coagulability.[5,6] A hypercoagulable state has been reported to be responsible for skin necrosis by formation of intravascular thrombi in small arteries,

[1]*Department of Surgery, Haeundae Paik Hospital, College of Medicine, Inje University, Busan, Republic of Korea.*

[2]*Department of Anesthesiology, Haeundae Paik Hospital, College of Medicine, Inje University, Busan, Republic of Korea.*

[3]*Department of Neurology, Haeundae Paik Hospital, College of Medicine, Inje University, Busan, Republic of Korea.*

Correspondence to: Jong Kwon Park, MD, Department of Surgery, Haeundae Paik Hospital, College of Medicine, Inje University, 1435 Jwa-Dong, Haeundae-Gu, Busan 612-080, Republic of Korea; E-mail: jkpark@paik.ac.kr

Ann Vasc Surg 2015; 29: 227–236
http://dx.doi.org/10.1016/j.avsg.2014.07.033

Manuscript received: January 4, 2014; manuscript accepted: July 28, 2014; published online: October 5, 2014.

Table I. Wagner classification of the 49 necrotic legs of 41 patients with critical limb ischemia

Wagner grade	Number of legs					
	I	II	III	IV	V	Total, *n* (%)[a]
Toe	12	2	2	12	3	31 (63)
Foot	1	0	0	2	4	7 (14)
Ankle	0	1	5	1	1	8 (16)
Calf	0	1	1	0	0	2 (4)
Thigh	0	0	0	0	1	1 (2)
Total, *n* (%)	13 (27)	4 (8)	8 (16)	15 (31)	9 (18)	49 (100)

[a]Thirty-three patients had unilateral necrosis and 8 patients had bilateral necrosis of the legs.

Table II. Comparison of the incidence of leg necrosis in gender, diabetes, hypertension, and smoking for all 103 patients

Variable	Number of all patients	Number of patients with leg necrosis, *n* (%)	*P* value[a]
Gender			
Male	92	35 (38)	0.339
Female	11	6 (54.5)	
Diabetes mellitus			
Yes	56	32 (57.1)	0.000
No	47	9 (19.1)	
Hypertension			
Yes	71	33 (46.5)	0.039
No	32	8 (25)	
Smoking			
Yes	92	34 (37)	0.109
No	11	7 (63.6)	

[a]Chi-squared test.

resulting in circulatory disturbances.[7–10] In patients with CLI, investigation of characteristic coagulation status changes associated with aging will be helpful for prevention and treatment of leg necrosis. In this study, we used preoperatively measured baseline clinical data in 103 patients with CLI to determine the interrelationships among aging, coagulation status, and leg necrosis.

MATERIAL AND METHODS

Between March 2010 and February 2013, 103 consecutive patients with CLI were enrolled in this study and treated. The diagnosis of CLI was based on clinical and physical examinations and computed tomography (CT) angiography (Aquilion ONE; Toshiba Medical Systems Corporation, Tochigi, Japan). All patients underwent ankle-brachial index test (VP-2000; Colin Corporation, Hayashi Komaki, Japan).

Table III. Comparison of serum creatinine levels between the critical limb ischemia patients with leg necrosis and those without necrosis in all 103 patients

Variable	Necrosis of limb	Number of patients	Serum creatinine (mean ± SD); mg/dL	*P* value[a]
Creatinine	Yes	41	1.6 ± 2.0	0.365
	No	62	1.3 ± 1.2	

SD, standard deviation.
[a]*t*-test.

Table IV. Comparison of age in gender, diabetes, hypertension, and smoking for all 103 patients with critical limb ischemia

Variable	Number of patients	Age (years), mean ± SD	*P* value[a]
Gender			
Male	92	66.7 ± 9.0	0.080
Female	11	71.6 ± 5.6	
Diabetes mellitus			
Yes	56	66.9 ± 8.7	0.705
No	47	67.6 ± 9.1	
Hypertension			
Yes	71	68.2 ± 8.3	0.115
No	32	65.2 ± 9.8	
Smoking			
Yes	92	66.8 ± 8.7	0.136
No	11	71.0 ± 9.4	

SD, standard deviation.
[a]*t*-test.

There was no patient who had known history of major trauma or venous diseases within 3 months before the enrollment in this study among the 103 patients.

This study was approved by the Institutional Review Board of Haeundae Paik Hospital, Inje University, and written informed consent was obtained from all study participants. CLI was defined clinically for all patients with chronic ischemic rest pain, ulcers, or gangrene attributable to objectively proven arterial occlusive disease by CT angiography.[1] According to the Trans-Atlantic Inter-Society Consensus Document on Management of Peripheral Arterial Disease II (2007), there are 2 recommended definitions for CLI.[1,11] The first one is recommendation 16, clinical definition of CLI in which patients with CLI are defined as all patients with chronic ischemic rest pain, ulcers, or gangrene attributable to objectively proven arterial occlusive disease. The other is recommendation 19, a clinical