Hypercoagulability predicts worse outcomes in young patients undergoing lower extremity revascularization

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ABSTRACT

Objective: Although we know that young patients with peripheral artery disease (PAD) have worse outcomes than older patients, there is a scarcity of information about the incidence of hypercoagulability in this population. Our aim was to analyze outcomes of young patients diagnosed with a hypercoagulable state (unusual tendency toward thrombosis) after lower extremity revascularization compared with similar patients without hypercoagulability.

Methods: All patients 50 years of age or younger undergoing an initial procedure for lower extremity PAD from 2000 to 2015 at the Cleveland Clinic were retrospectively analyzed. Patients with a hypercoagulability panel were included and classified into groups as hypercoagulable positive (HP) or hypercoagulable negative (HN). Demographics, preoperative risk factors, form of presentation, level of disease, and type of intervention were analyzed in addition to perioperative complications, early failure, and length of stay. Primary outcomes were limb loss and primary, primary assisted, and secondary patencies. Outcomes were analyzed and Kaplan-Meier curves generated.

Results: Ninety-one patients were included for a total of 118 limbs. Mean follow-up was 32 months; 55% of patients had a hypercoagulable disorder, with 59% having lupus anticoagulant and 32% hyperhomocysteinemia. In the HP group, 71% were men; 49% were men in the HN group. Patients overall had a high prevalence of smoking (86%), hypertension (36%), and hyperlipidemia (33%). Acute limb ischemia was the most common form of presentation for both groups (50% HP, 38% HN). The aortoiliac segment was the most commonly affected (38% HP, 50% HN). The most frequent operation in the HN group was endarterectomy or bypass (32%); in the HP group, it was an endovascular intervention (29%). Perioperative occlusion or failure was 18% in the HN group vs 30% in the HP group ($P > .05$). Primary patency, primary assisted patency, and secondary patency at 36 months were all better for the HN group (no statistical significance) in all treatment groups. Major amputation at 36 months was significantly worse for the HP group (40% vs 10% in the HN group; $P < .005$). There was no difference in perioperative complications or length of stay.

Conclusions: Young patients undergoing lower extremity revascularization for PAD have worse outcomes when associated with hypercoagulability. There are trends to decreased patency of revascularization in these patients, with significantly more major amputations. No clear differences between modalities of treatment were demonstrated. (J Vasc Surg 2018;■:1-6.)

Keywords: Hypercoagulability; Thrombophilia; Peripheral artery disease

Peripheral artery disease (PAD) is an increasingly prevalent health problem. Typically associated with general cardiovascular risk factors, age plays an important role, with an estimated prevalence as high as 12% in people 60 years of age or older.[1] PAD in younger patients can also be due to different causes; however, atherosclerosis remains the leading cause.[2] Other less common causes include arteritis and developmental anomalies, among others.[3] A hypercoagulable state (unusual tendency toward thrombosis)[4] is recognized as an important cause of extremity ischemia with rates around 15% to 30% in this subset of patients.[5] As a whole, hypercoagulable disorders have a well-known widespread association with venous thromboembolic disease and to a lesser degree have been linked to arterial thrombosis. In addition, failure of multiple arterial procedures is anecdotally presumed to be related to undiagnosed hypercoagulable states. There is a scarcity of information about this group of young patients with PAD, with some reports suggesting a significantly worse outcome for patients with diagnosed hypercoagulable disorders.[6]

The purpose of this study was to evaluate outcomes of lower extremity revascularization in young patients with or without a diagnosed hypercoagulable disorder, aiming to identify factors that affect their outcomes. We also evaluated different treatment modalities (endovascular and open) to identify differences that may improve patency outcomes and limb salvage.

METHODS

The study was presented to and approved by our local Institutional Review Board. We retrospectively reviewed data for all patients 50 years of age or younger with an available hypercoagulability panel (initially ordered at

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the discretion of the treating surgeon) who underwent a first lower extremity revascularization procedure between 2000 and 2015 at the Cleveland Clinic Foundation. An unidentified database was used, so no consent was required. Patients with known chronic kidney disease on dialysis, ischemia secondary to trauma, aortic dissection, cardiac source of embolization, or entrapment syndromes were excluded from the study.

Patients were separated into two groups: hypercoagulable positive (HP), patients with a proven serologically hypercoagulable state; and hypercoagulable negative (HN), patients without a hypercoagulable state. Electronic databases and charts were reviewed, images were analyzed, and a database was compiled. In cases in which a patient had a contralateral extremity intervention during the study period, each limb was considered separately for the analysis.

Demographic data and preoperative risk factors were analyzed. Initial presentation was classified as claudication, critical limb ischemia, or acute limb ischemia (ALI). The ankle-brachial index was recorded if available. Level of disease was also captured and labeled aortoiliac, femoropopliteal, or tibial disease. The type of surgery was classified as endovascular, endarterectomy or bypass, hybrid, embolectomy, or catheter-directed thrombolysis (CDT). Primary outcomes were primary patency, primary assisted patency, secondary patency, and major limb loss, reported according to the Society for Vascular Surgery standards.[7] Secondary end points were complications, length of stay, and early failure.

Hypercoagulability studies reviewed included lupus anticoagulant (LAC), anticardiolipin antibodies, hyperhomocysteinemia, factor V Leiden, protein C or protein S deficiency, and prothrombin 20210 gene mutation. Antithrombin III deficiency was not considered, given its low specificity.

Statistical analysis. Statistical analysis was performed with comparisons between groups using logistic regression with generalized estimating equations (GEE) or mixed-effects models to account for patients with bilateral limb interventions. Patency outcomes were evaluated using marginal Cox proportional hazards models. Patients with CDT or embolectomy alone and no other revascularization strategies were excluded. Other outcomes were compared using logistic regression with GEE for nominal measures or proportional odds regression with GEE for ordered measures. Analyses were performed using SAS software (version 9.4; SAS Institute, Cary, NC). A significance level of .05 was assumed for all tests.

RESULTS

Ninety-one patients fulfilled inclusion criteria, with a total of 118 limbs. Mean follow-up was 32 months (0-16 years), with 32% of patients lost to follow-up after 2 years. Overall, 55% of patients presented with a positive hypercoagulability panel. Table I summarizes hypercoagulability panel findings, with the majority of patients presenting with LAC (59%), followed by hyperhomocysteinemia (32%) and factor V Leiden (13.8%).

When analyzing the differences between groups, we did not find differences in age (mean age of both groups, 42 years). Whereas there was a noticeable trend for more frequent HP in men (71% vs 49% for HN), this did not reach statistical significance ($P = .06$).

As expected, overall there was a high incidence of smoking (86%), hypertension (36%), hyperlipidemia (33%), and coronary artery disease (25%) without statistically significant differences between groups (Table II). The HP group had more episodes of previous thromboembolic events at 34% vs 8% for the HN group ($P = .02$).

The most common form of presentation was ALI in 38% and 50% of the HN and HP groups, respectively, followed by critical limb ischemia in 36% and 39%. We found 15% of ALI patients with underlying PAD, with no difference between groups. Rutherford classification showed 40% of patients classified as stage III, 20% stage IV, and 20% stage V and stage VI, with no difference between groups. Mean ankle-brachial indices were not significantly different at 0.49 for the HN group and 0.54 for the HP group. The aortoiliac level was the most commonly affected segment in both groups at 38% in the HP group and 50% in the HN group, followed by the

ARTICLE HIGHLIGHTS

- **Type of Research:** Retrospective cohort study
- **Take Home Message:** In 91 patients younger than 50 years with peripheral artery disease, many presenting with acute limb ischemia, those with a hypercoagulable state (55%) had a higher amputation rate at 36 months than those without (40% vs 10%). There was also a trend toward higher perioperative thrombosis rates and poorer 3-year patency.
- **Recommendation:** Young peripheral artery disease patients with hypercoagulability, especially when presenting with acute limb ischemia, are at higher risk for major amputation regardless of treatment modality.

Table I. Hypercoagulability panel summary (N = 65)

Factor	No. (%)
LAC	38 (58.5)
Hyperhomocysteinemia	21 (32.3)
Factor V Leiden	9 (13.8)
Anticardiolipin antibodies	8 (12.3)
Prothrombin gene	6 (9.2)
Protein C or S deficiency	6 (9.2)

LAC, Lupus anticoagulant.

Table II. Group comparison

	HN group (n = 53)	HP group (n = 65)	*P* value
Age, years	42.2 ± 8.0	42.8 ± 6.7	.65
Female sex	27 (50.9)	19 (29.2)	.068
Hypertension	20 (37.7)	23 (35.4)	.68
Diabetes mellitus	12 (22.6)	19 (29.2)	.14
Hyperlipidemia	17 (32.1)	21 (32.8)	.64
Coronary artery disease, CABG or PCI	12 (22.6)	18 (27.7)	.36
COPD	2 (3.8)	5 (7.7)	.20
Cerebrovascular accident	4 (7.8)	8 (12.3)	.53
Cancer	3 (5.7)	7 (10.8)	.40
Smoker	44 (89.8)	52 (83.9)	.89
ALI	20 (37.7)	32 (50.0)	.46
Critical limb ischemia	19 (35.8)	25 (39.1)	.72
Claudicant	14 (26.4)	13 (20.3)	.52
ABI of involved leg	0.49 ± 0.25	0.54 ± 0.25	.40
Surgery type			.70
Hybrid	3 (5.7)	3 (4.6)	
Endovascular	10 (18.9)	19 (29.2)	
Endarterectomy or bypass	17 (32.1)	16 (24.6)	
CDT	16 (30.2)	13 (20.0)	
Embolectomy	7 (13.2)	14 (21.5)	

ABI, Ankle-brachial index; *ALI,* acute limb ischemia; *CABG,* coronary artery bypass graft; *CDT,* catheter-directed thrombolysis; *COPD,* chronic obstructive pulmonary disease; *HN,* hypercoagulable negative; *HP,* hypercoagulable positive; *PCI,* percutaneous coronary intervention.
Statistics are presented as mean ± standard deviation with mixed-effects model *P* value or number (column %) with generalized estimating equations *P* value.

Table III. Perioperative outcomes

	HN group (n = 53)		HP group (n = 65)		
Factor	No.	Statistics	No.	Statistics	*P* value
Length of stay postoperatively	47	5.0 (3.0-7.0)	49	6.0 (4.0-13.0)	>.05
Perioperative complication	42	19 (45.2)	51	15 (29.4)	>.05
Perioperative reintervention	53	19 (35.8)	63	30 (47.6)	>.05
Perioperative major amputation	51	3 (5.9)	63	10 (15.9)	>.05
CDT success	16	11 (68.8)	13	5 (38.5)	>.05

CDT, Catheter-directed thrombolysis; *HN,* hypercoagulable negative; *HP,* hypercoagulable positive.
Statistics are presented as median (25%-75%) or number (column %) with generalized estimating equations *P* values or marginal Cox proportional hazards model.

femoropopliteal segment (48% HP, 38% HN) and tibial segments (14% HP, 11% HN).

In terms of surgery, the most common operation performed in the HN group was endarterectomy or bypass (32%), followed by CDT (30%); in the HP group, the leading treatment was endovascular (29%), followed by endarterectomy or bypass (25%). The type of surgery was further evaluated by level. In the aortoiliac segment, the most common intervention was the endovascular approach at 33% (44% HP, 22% HN), followed by combination of aortic bypass or endarterectomy (12% HP, 30% HN); embolectomy and CDT were performed in 20% of each group. The femoropopliteal segment was primarily treated with bypass or endarterectomy in 39% of cases (35% HP, 45% HN), followed by CDT, endovascular intervention, and embolectomy in 20% of cases. Finally, tibial segments were mainly treated with CDT in 53% of cases (44% HP, 67% HN), followed by endovascular treatment in 20% and bypass and embolectomy in 13% each. There was no statistical difference between groups.

Perioperative outcomes. Patients in both groups exhibited similar total hospital length of stay (5 days in the HN group and 6 days in the HP group; Table III). Perioperative complications were more common in patients in the HN group (45% vs 30%), with no statistical significance. Overall complications in both groups were occlusion or worsening ischemia in 50% (25 cases),

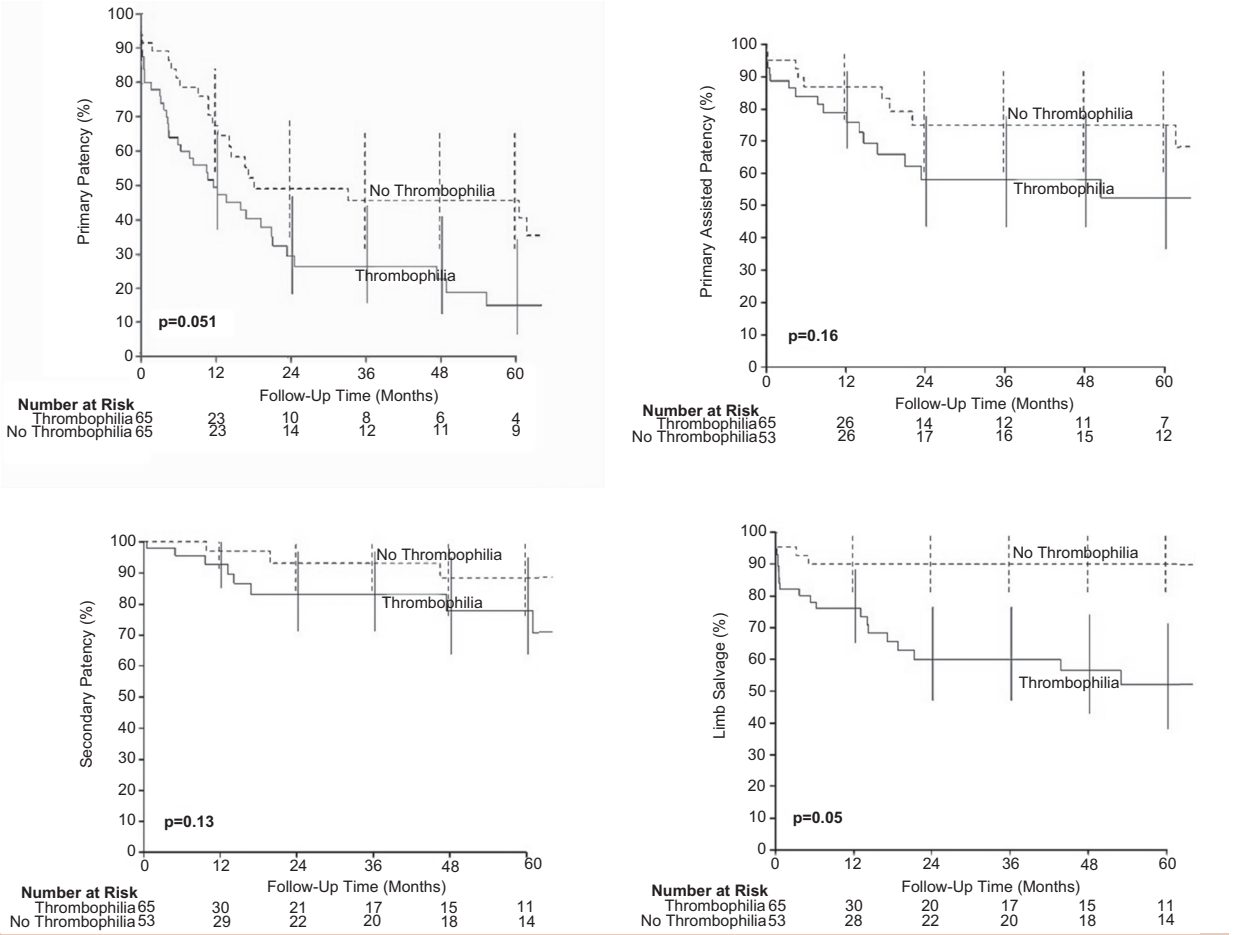

Fig. Comparison of primary patency, assisted primary patency, secondary patency, and limb salvage in patients with or without thrombophilia.

followed by wound infection in 14% and perioperative bleeding or hematoma in 10%. There were three cases of new perioperative arterial thrombosis despite early adequate anticoagulation and two cases of new venous thromboembolism. There were no cardiac events in this series.

Perioperative immediate occlusion or failure to achieve revascularization was 18% in the HN group vs 30% in the HP group (P = NS). Perioperative reinterventions (48% vs 36%) and major perioperative amputations (16% vs 6%) were more frequent in the HP group; however, none of this achieved statistical significance.

Looking at the primary end point, overall primary patency at 36 months was 45.6% for the HN group compared with a lower 26.5% for the HP group (P = .051; Fig). For patients who underwent bypass procedures at any level of disease, 12-month primary patency was 38% in the HP group compared with 64% in the HN group (P = NS). Endovascular procedures had 12-month primary patency of 40% in the HP group vs 50% in the HN group (P = NS).

Primary assisted patency and secondary patency at 36 months were 74.9% vs 52.4% and 93.2% vs 83.2% for the HN group compared with the HP group (P = NS), similar in comparing bypass or endovascular interventions in both groups. Major amputation at 36 months was the only statistically significant difference at 40% for the HP group vs 10% for the HN group ($P < .005$). CDT success varied between groups, with almost 69% success in the HN group vs only 39% in the HP group ($P > .05$). The Fig shows Kaplan-Meier curves for each of these outcomes.

DISCUSSION

Young patients with PAD tend to have a dismal cardiovascular prognosis with poor outcomes and high rates of progression.[2] These are associated with high rates of comorbidities that further worsen this accelerated atherosclerosis process.[8] In our series, we confirmed these findings, with high rates of hypertension (36%), diabetes mellitus (26%), coronary artery disease (25%), and smoking (87%) in this younger population. Overall, we also found poor outcomes with higher numbers of reinterventions and limb loss.

A hypercoagulable state is a known risk factor for thromboembolic events, with the majority of data

showing venous compromise; however, some specific hypercoagulable disorders have been linked to arterial thrombosis. These include LAC and hyperhomocysteinemia as the main serologic abnormalities encountered in stroke and coronary artery disease patients.[9-11] Similarly, the most common hypercoagulable disorder encountered in our series was LAC (59%), followed by hyperhomocysteinemia (32%).

Previous studies have shown hypercoagulable disorders to be an uncommon finding in sampling of the broad PAD population, with rates around 10%.[12] However, data from Eldrup-Jorgenson et al[13] specifically in younger populations led us to suspect that hypercoagulable disorders are largely underappreciated. They found that when directed to young patients with PAD, hypercoagulability rates are higher with variation from 13% (when studies are ordered selectively on the basis of clinical suspicion) to 50% (when there is a protocol to sample every patient). In concordance with this, more than half of the patients in our series (55%) had a hypercoagulable disorder on laboratory workup. Because this was performed at the physician's discretion, there may still be under-reporting within this population. Based on our results, it might be valuable to obtain a hypercoagulable panel specifically to help establish a realistic prognosis.

There are reports that confirm significantly worse outcomes in this subset of young patients with hypercoagulability when faced with lower extremity interventions for PAD.[6,14] In our study, we observed worse outcomes in hypercoagulable patients, with a statistically significant increase in limb loss at 3 years with rates up to 40%. This group of patients also exhibited more perioperative occlusions, interventions, and amputations.

Some reports have suggested that endovascular procedures have worse outcomes than open surgery in young patients.[14] Based on our study, it is not clear which surgical approach is superior, with similar outcomes between endovascular intervention and open surgery. However, we noticed a decrease of success rates of CDT in the HP group that could indicate favorability of open thrombectomy in patients with hypercoagulability presenting with ALI. The proportion of endovascular cases at the aortoiliac level and endarterectomy or bypass at the femoropopliteal level suggests that surgical decision-making is primarily based on known general procedural outcomes.

Our study is limited in several ways. We have a highly selected population with hypercoagulability testing done on the basis of the individual physician's judgment; thus, true prevalence conclusions cannot be obtained because not all potential patients were screened. This is also a single-center, retrospective study, with a relatively insufficient number of patients to uncover statistical differences between treatment modalities or to assess physician bias.

CONCLUSIONS

This study represents an addition to the limited literature in this area. Hypercoagulable disorders continue to have a negative impact on outcomes of lower extremity revascularization in young patients. Limb loss rate is higher in this subset of patients. Strategies to mitigate this effect are yet to be identified to further direct best surgical and medical practice. In general, a hypercoagulable disorder should be included within the differential diagnosis of patients younger than 50 years presenting with limb ischemia or with early failure of PAD interventions. Further studies in this area are needed to preoperatively identify patients at risk and to develop strategies for appropriate use of laboratory screening.

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AUTHOR CONTRIBUTIONS

Conception and design: JT, RK
Analysis and interpretation: JT, MO, RK
Data collection: JT
Writing the article: JT, RK
Critical revision of the article: JT, MO, RK
Final approval of the article: JT, MO, RK
Statistical analysis: Not applicable
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Overall responsibility: JT

REFERENCES

1. Lane JS, Vittinghoff E, Lane KT, Hiramoto JS, Messina LM. Risk factors for premature peripheral vascular disease: results for the National Health and Nutritional Survey, 1999-2002. J Vasc Surg 2006;44:319-25.
2. McCready RA, Vincent AE, Schwartz RW, Hyde GL, Mattingly SS, Griffen WO Jr. Atherosclerosis in the young: a virulent disease. Surgery 1984;96:863-8.
3. Pairolero PC, Joyce JW, Skinner CR, Hollier LH, Cherry KJ Jr. Lower limb ischemia in young adults: prognostic implications. J Vasc Surg 1984;1:59-64.
4. World Health Organization. Inherited thrombophilia: report of a joint WHO/International Society of Thrombosis and Haemostasis (ISTH) meeting. Geneva, Switzerland: World Health Organization; November 6-8, 1995.
5. Levy PJ, Hornung CA, Jaynes JL, Rush DS. Lower extremity ischemia in adults younger than forty years of age: a community-wide survey of premature atherosclerotic arterial disease. J Vasc Surg 1994;19:873-81.
6. Curi MA, Skelly CL, Baldwin ZK, Woo DH, Baron JM, Desai TR, et al. Long-term outcome of infrainguinal bypass grafting in patients with serologically proven hypercoagulability. J Vasc Surg 2003;37:301-6.
7. Stoner MC, Calligaro KD, Chaer RA, Dietzek AM, Farber A, Guzman RJ, et al. Reporting standards of the Society for Vascular Surgery for endovascular treatment of chronic lower extremity peripheral artery disease. J Vasc Surg 2016;64:e1-21.
8. Levy PJ, Gonzalez FG, Hornung CA, Chang WW, Haynes JL, Rush DS. A prospective evaluation of atherosclerotic risk factors and hypercoagulability in young adults with premature lower extremity atherosclerosis. J Vasc Surg 1996;23:36-45.

9. Nygård O, Nordrehau JE, Refsum H, Ueland PM, Farstad M, Vollset SE. Plasma homocysteine levels and mortality in patients with coronary artery disease. N Engl J Med 1997;337:230-6.
10. Levine SR, Salowich-Palm L, Sawaya KL, Perry M, Spencer HJ, Winkler HJ, et al. IgG anticardiolipin antibody titer >40 GPL and the risk of subsequent thrombo-occlusive events and death. A prospective cohort study. Stroke 1997;28:1660-5.
11. Sofi F, Lari B, Rogolino A, Marcucci R, Pratesi G, Dorigo W, et al. Thrombophilic risk factors for symptomatic peripheral arterial disease. J Vasc Surg 2005;41:255-60.
12. Curi M, Donaldson MC, Weinberg DS, Belkin M, Whittemore AD, Mannick JA. Screening for hypercoagulable states in vascular surgical practice: a preliminary study. J Vasc Surg 1990;11:825-31.
13. Eldrup-Jorgensen J, Flanigan P, Brace L, Sawchuk AP, Mulder SG, Anderson CP, et al. Hypercoagulable states and ischemia in young adults. J Vasc Surg 1989;9:334-41.
14. Ochoa Caar CI, Makaroun MS, Marone LK, Rhee RY, Al-Khoury G, Cho JS, et al. Impact of endovascular options on lower extremity revascularization in young patients. J Vasc Surg 2012;56:703-13.

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