Embolization During Popliteal and Tibial Intervention for CLTI

A look at the incidence and impact on outcomes.

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Chronic limb-threatening ischemia (CLTI) is a steadily rising vascular threat due to globally increasing rates of diabetes mellitus and chronic kidney disease, affecting nearly 1% to 2% of people worldwide and > 10% of patients with peripheral artery disease (PAD) and resulting in 300 to 500 major nontraumatic amputations each day in the United States.[1] CLTI often remains undiagnosed until late in its course. One consequence of this is that fewer than half of patients receive an appropriate vascular evaluation prior to undergoing an above-ankle amputation.[2] Endovascular therapies continue to evolve for the treatment of popliteal and infrapopliteal occlusive disease, with recent data showing favorable limb salvage rates with coordinated care models, vascular intervention, and diligent surveillance-driven reintervention.[3-6] Despite this, there are unique challenges to CLTI procedures that have limited the widespread adoption of these techniques, including complex anatomic patterns of dense calcification and chronic total occlusion (CTO), nonreconstructible vascular beds with impaired or absent pedal circulation, procedure-related arterial dissection, recoil and early restenosis, and distal embolization. Over the past decade, these challenges have spawned the development of many new and investigational technologies to improve outcomes, including the Tack endovascular system (Philips) and other dedicated tibial scaffolds,[7-10] arteriovenous flow reversal and deep venous arterialization tools,[11] and devices specific to treating calcium.[5,12] For distal popliteal and tibiopedal arterial interventions, there remains one dominant procedural and clinical problem that has not been well studied and for which there are no dedicated solutions: procedure-related embolization.

THE CLINICAL SPECTRUM OF EMBOLIZATION DURING CLTI PROCEDURES

- Anatomic cutoff
- No/slow flow
- Perfusion deficits
- Loss of wound blush and worsening transcutaneous oxygen pressure/skin perfusion pressure
- Delayed wound healing
- Repeated procedures (progressive loss of runoff)
- Unplanned amputation

Procedure-related embolization during CLTI interventions is a frequent but not well-assessed problem and encompasses a broad spectrum of possible injury and consequences (Sidebar). In a recent study of distal embolic protection during superficial femoral artery interventions, captured debris of < 1 mm was noted in 98% of cases, 1 to 2 mm in 22% of cases, and > 2 mm in 9% of cases.[13] Because the smallest pore size of distal embolic protection filters is 110 µm, embolization of nonaggregated, smaller-sized material may be overlooked. In CLTI, because of the unique characteristics of infrapopliteal CTOs, longer lesions, and calcification, the propensity for embolization is potentially greater than

TABLE 1. EMBOLIZATION EVENT RATES

Event	Study	Group	n	%	Parameter/Notes
Angiographic	LIBERTY[6]	R2-3	247	6.5	–
		R4-5	287	5.6	–
		R6	74	8.1	–
	Ward et al[18]	BTK SpiderFX embolic protection device (Medtronic)	36	47	Captured debris
	PRIME[19]	R3-5	389	1.5	–
Slow/no flow	LIBERTY[6]	R2-3	247	0.4	–
		R4-5	287	1.6	–
		R6	74	1	–
	Tokuda et al[20]	R5-6	161	18.6	–
	CONFIRM[21]	BTK	1,708	7.7	–
Major unplanned amputation	NCDR[22]	CLI	12,588	7.04	–
	VQI[23]	PTA	6,094	5.23	49% CLTI
		Stent	4,032	2.95	53% CLTI
		ATH	3,312	3.49	55% CLTI
Perfusion	Settembre et al[24]	CLI	104	8.8	IGFA
	Mironov et al[25]	CLI	–	39	IGFA

Abbreviations: ATH, atherectomy; BTK, below the knee; CLI, critical limb ischemia; CLTI, chronic limb-threatening ischemia; IGFA, indocyanine green fluorescent angiography; NCDR, National Cardiovascular Data Registry; percutaneous transluminal angioplasty; R, Rutherford class; VQI, Vascular Quality Initiative.

in other vascular beds. Previous data have suggested that these more complex features of occlusions and lesion length are associated with higher rates of distal embolization.[14] Embolization has been demonstrated to be an important cause of compromised runoff after vascular procedures, which directly correlates with recurrent symptoms, repeat interventions, and limb loss.[15] Importantly, the concept of "clinically relevant" embolization, as defined by clinician or core lab identification of a newly recognized abrupt distal vessel cutoff, is the most obvious example of embolic occlusion but likely represents only a small fraction of the microembolization occurring during procedures that affects the smaller arteries of the foot, pedal arterioles, and capillaries. In fact, for femoropopliteal interventions, angiographic evidence of embolization represents only 5% of emboli identified using microscopic identification of embolic protection filters.[16] Consequently, microembolization has not been well studied, in effect acknowledged as an acceptable occurrence in limb salvage procedures. It is striking that despite the tremendous advances in vascular care over the last 25 years, there is an obvious paucity of data regarding the exact definition of embolization, the frequency of worsening perfusion parameters after CLTI treatments, the best modalities for measuring oxygen delivery to dermal and wound tissues, the content of embolic material (eg, plaque, cholesterol, thrombus, cellular), or the best modes of prevention and treatment of this condition. As the incidence and prevalence of diabetes increases and the vast majority of patients presenting with CLTI have diabetes, the pedal microcirculatory occlusive disease present in these patients makes them particularly susceptible to the negative consequences of intraprocedural embolization, even when this phenomenon is not readily apparent.

THE MICROEMBOLIZATION PHENOMENON

There is evidence that microscopic material liberated downstream during endovascular procedures is a common event and cause of unfavorable short- and longer-term outcomes (Table 1).[6,17-25] Within the spectrum of adverse events of embolization, this is seen in the wide range of clinical implications, including postprocedural pain and blistering (ie, livedo reticularis), additional unplanned thrombectomy or thrombolytic procedures, acute worsening ischemia, repeat interventions (and their associated radiation exposure, contrast load, and cost),

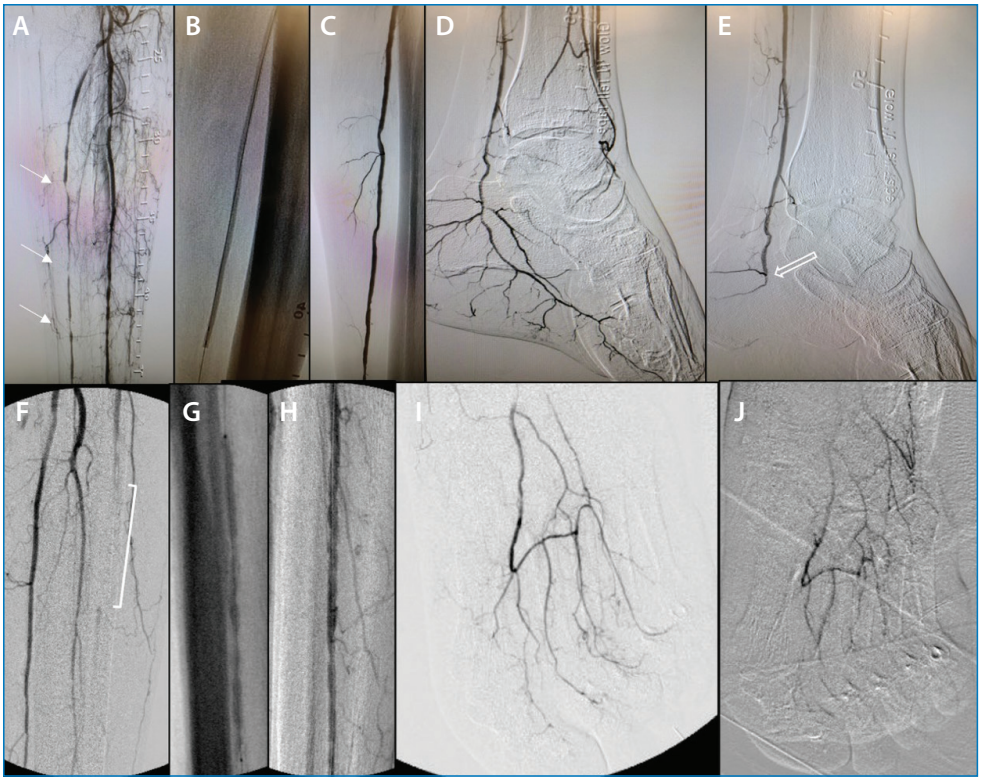

Figure 1. Patterns of embolization. Macroembolization occurring with posterior tibial artery stenosis (arrows) (A) treated with angioplasty alone (B, C). Baseline pedal angiography (D) compared with postprocedural abrupt embolic arterial cutoff of the common plantar artery (open arrow) (E). Microembolization occurring with anterior tibial artery CTO (brackets) (F) treated with atherectomy and angioplasty (G, H). Baseline (I) compared with marked reduction in visualized digital arteries at completion (J).

and microcirculatory injury. The latter is particularly alarming and can be a substantial cause of described complications, including slow or no reflow, compromised perfusion, delayed or absent wound healing, unplanned amputation, and limb loss (Figure 1). Improved ankle-brachial indices after revascularization do not correlate with improvements in microcirculation as measured by transcutaneous oxygen tension measurements, reflecting differences in assessing procedural outcomes in large versus small arteries of the foot.[26] The observed phenomenon of delayed increase in measurable perfusion,[26] as well as cases in which there is no hemodynamic improvement after treatment, may often be due to embolization, with data suggesting that patients without immediate clinical improvement do poorly in terms of limb salvage.[12] Finally, in a study of 161 patients with CLTI undergoing tibiopedal angioplasty, a "slow-flow" angiographic pattern was seen in 18.6%, was more common in the presence of severe calcification and CTO, and was associated with lower wound healing rates (1-year wound healing, 57% vs 77%) and major amputation (1-year amputation-free rate, 60% vs 88%) compared to patients with an absence of slow flow.[27] Slow flow is also associated with lower postintervention skin perfusion pressures.[20]

Unplanned rehospitalization occurs in > 15% of patients with PAD and CLTI, predominantly due to pedal sepsis or wound worsening. Almost one-quarter of these readmitted patients undergo an additional revascularization procedure (8.2%) or major amputation (11.7%).[28] In a study of 8,726 patients from the Eastern Vascular Society, 421 (4.8%) of CLTI patients underwent unplanned amputation within 30 days of an index procedure.[29] An analysis of 13,258 patients undergoing tibiopedal interventions using Medicare data reported progressive gangrene as the most common limb-based cause for hospital readmission (37%), with 44% undergoing minor or major amputation.[30] In the EUCLID study, which compared monotherapy with ticagrelor or clopidogrel, the risk of limb deterioration was fourfold higher in patients with prior revascularization.[31]

Perfusion imaging (including indocyanine green imaging [IGI], transcutaneous oxygen tension measurements, and skin perfusion pressure) provides a unique method to assess otherwise potentially unrecognized procedural microemboli and is a valuable surrogate due to the recognized correlation between these parameters and limb outcomes.[32-34] This is supported by recent evidence that microvascular disturbance is associated with major amputation.[35] In a study of patients (104 limbs) undergoing open or endovascular revascularization, 8.8% of patients had worse IGI parameters despite technically successful revascularization.[24] Mironov et al

found decreased ingress rates into the foot on IGI in 39% of patients treated with angioplasty and stenting, with more than one-half in the infrapopliteal distribution.[25] Of note, Colvard et al noted that embolic events detected using laser-assisted fluorescence imaging may not be visible by conventional angiography.[36] In a smaller evaluation of 14 patients undergoing continuous near-infrared spectroscopy measurements of foot oxygenation during endovascular treatment for CLTI, five (35%) patients showed acute deterioration at procedure completion, although parameters did improve on 4-week evaluation.[37] Although clinical outcomes were not reported, these findings suggest acute embolic injury during these procedures.

PARTICULATE EMBOLIZATION FROM DRUG-COATED DEVICES

The increased clinical utility of drug-coated and drug-eluting devices has transformed interventional medicine but may provide a unique hazard for below-the-knee interventions. The occurrence of polymer-related embolization has been well described as an "elusive" and possibly pernicious event.[38] For patients who underwent intervention with drug-coated balloons (DCBs) (and possibly drug-eluting stents), particulate embolization of polymer or paclitaxel into wound beds creates a dual pathway of damage due to physical obstruction plus antiproliferative effects in vulnerable tissues, resulting in delayed healing and potentially a higher risk of amputation. In a swine study, Granada et al found dose-related paclitaxel particulate embolization in limb wound beds, although healing and epithelialization in these healthy subjects were not inhibited.[39] In contrast, in the IN.PACT DEEP trial, higher rates of amputation were observed with the use of DCBs compared with traditional balloons.[40] Clearly, more investigation of microcirculatory effects is needed to better understand the potential downstream tissue effects of both antiproliferative-coated devices as well as their polymer excipients.

CONCLUSION

Despite improvements in revascularization for CLTI over the past decade, clinical success may be limited by unrecognized procedural embolization. The assessment of treatment endpoints has historically focused on angiographic findings, with an inherent underappreciation of microcirculatory damage. Because most CLTI patients have preexisting microcirculatory compromise, they are especially vulnerable to procedure-related embolization, which may limit clinical improvement or promote further clinical deterioration despite successful revascularization. Further efforts to quantify and find solutions to this limitation of limb salvage procedures can potentially improve outcomes for these patients. ■

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