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Review Article

Current Perspective on Hemodialysis Patients with Peripheral Artery Disease

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The prevalence of peripheral artery disease is substantially higher in patients on chronic hemodialysis than in the general population. The presence of calcified lesions characteristic of hemodialysis patients has an adverse influence on the initial success and long-term outcomes of both surgical bypass and endovascular therapy. Although the selection of revascularization strategy depends on whether an autologous vein is available and if the patient has a life expectancy of at least two years, it is difficult to predict the life expectancy in a real-world clinical situation. Endovascular therapy may be appropriate for many hemodialysis patients with poor general condition because of the high risk of perioperative complications and the poor long-term prognosis. Deciding which treatment option is more appropriate should be done on a case-by-case basis, especially in hemodialysis patients with critical limb ischemia.

Keywords: hemodialysis, peripheral artery disease, endovascular therapy

Epidemiology of Peripheral Artery Disease

The prevalence of peripheral artery disease (PAD) is substantially higher in patients on chronic hemodialysis (HD) than in the general population. It has been estimated as approximately 15%–23% when defined by assessment of symptoms and past history or 16.6%–38.3% when defined by an ankle-brachial index <0.9.[1] The following predictors of PAD have been reported in dialysis patients: advanced age (odds ratio [OR]: 1.15/age), male sex (OR: 1.26), diabetes (OR: 4.18), current smoking (OR: 1.27), coronary artery disease (OR: 2.85), duration of dialysis (OR: 1.13/year), undernutrition (OR: 0.67/g), diastolic blood pressure before dialysis (OR: 0.91/10 mmHg), and parathyroid hormone level (OR: 0.96).[2] As the stage of chronic kidney disease becomes more advanced, the initial symptoms of PAD tend to be more severe, and dialysis patients more frequently present ischemic ulceration/gangrene than rest pain[3] (**Fig. 1**). A systematic review of 48,000 patients identified the following predictors of foot ulceration in dialysis patients: previous foot ulceration (OR: 17.56), PAD (OR: 7.52), diabetes (OR: 3.76), peripheral neuropathy (OR: 3.24), coronary artery disease (OR: 3.92), retinopathy (OR: 3.03), previous amputation (OR: 15.50), and elevated serum phosphorus level (mean difference [MD]: 0.40 mg/dL). In addition, the predictors of lower limb amputation in dialysis patients were: previous foot ulceration (OR: 70.13), PAD (OR: 9.12), diabetes (OR: 7.48), peripheral neuropathy (OR: 3.36), coronary artery disease (OR: 2.49), male sex (OR: 1.50), current smoking (OR: 2.26), and high glycated hemoglobin level (MD, 0.75%).

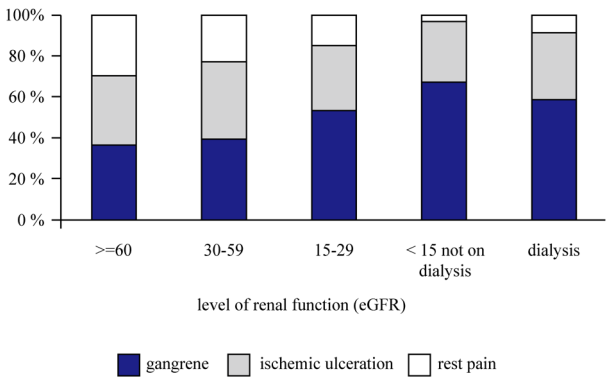

Fig. 1 Presentation at time of initial diagnosis of critical limb ischemia by level of renal function. As the stage of chronic kidney disease becomes more advanced, the initial symptoms of PAD tend to be more severe, and dialysis patients more frequently present ischemic ulceration/gangrene than rest pain.

Distribution of Lesions

It has been reported that advanced renal failure is associated with an increased frequency of complex distal lower limb lesions. In patients with renal failure, the frequency of femoral popliteal lesions is 3.64 times higher than that of aortoiliac lesions, while the frequency of infrapopliteal

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lesions is 7.72 times higher.[4] In patients on HD, vascular calcification becomes more severe as the Fontaine class increases.[5] Calcified arterial lesions can be plaque with calcium deposits in the intima or Mönckeberg's medial calcification, which is annular deposition of calcium in the tunica media of a muscular artery. The presence of calcified lesions has an adverse influence on the initial success and long-term results of both surgical bypass and endovascular therapy (EVT).

Revascularization Strategy

PAD in HD patients can be characterized as follows: 1) the initial symptom is occasionally critical limb ischemia (CLI), especially toe ulceration, 2) symptomatic patients tend to have multiple infrainguinal lesions (affecting the femoral artery, popliteal artery, and leg arteries), and 3) lesions often show calcification of the intima and media. These patients require a therapeutic strategy that incorporates active examination and early detection with selection of treatment based on the disease characteristics in each case. EVT is performed to dilate lesions, but its effects vary considerably according to the extent of stenosis and the features of the lesions. In particular, EVT using a balloon catheter and stenting is unlikely to achieve initial success due to suboptimal dilatation in patients with heavily calcified lesions. Also, the long-term patency generally decreases as the vessel diameter decreases. Thus, the femoral and popliteal arteries have a smaller diameter than the iliac artery, and the long-term patency achieved with EVT is lower for lesions in these vessels. Accordingly, HD patients with PAD and severely calcified lesions would seem to be particularly unsuitable for EVT. Nonetheless, EVT is widely used to treat PAD in patients on HD because perioperative complications are more frequent after surgical revascularization than after EVT, and the long-term limb salvage rate is clinically acceptable since the life expectancy of these patients is limited. That is, surgical bypass achieves superior long-term patency to EVT but provides less benefit for HD patients due to their shorter life expectancy compared to non-HD patients.

It has been reported that the 30-day postoperative mortality rate is high (18%) after surgical revascularization in HD patients with CLI.[6] Major causes of death are cardiac, including acute myocardial infarction and heart failure. According to a recent report, the 30-day postoperative mortality after infrainguinal bypass was 9% in HD patients with CLI. The prognosis for the lower limb in those patients is reasonable, with a one-year patency of 66% and a one-year limb salvage rate of 89%, but the overall prognosis is inferior with a one-year survival rate of only 68% and an amputation-free survival rate of 64%.[7] A meta-analysis of infrainguinal arterial reconstruction in patients with end-stage renal disease showed relatively good results for the lower limb, since the patency rate was 74.9% at one year and 69.8% at two years, while the limb salvage rate was 84.2% and 74.7%, respectively. Conversely, the survival rate was only 71.6% at one year and 53.3% at two years, which was worse than both the patency rate and the limb salvage rate[8] (**Fig. 2**).

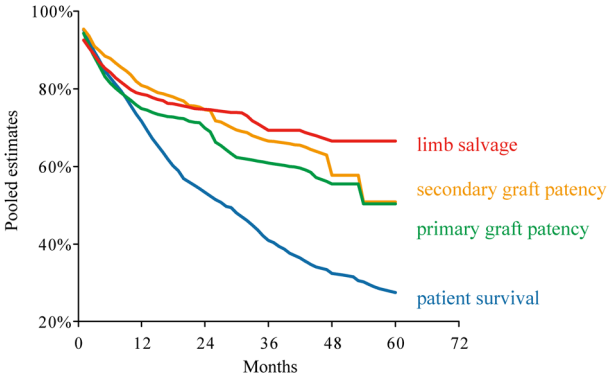

Fig. 2 A meta-analysis of infrainguinal arterial reconstruction in patients with end-stage renal disease. The patency rate was 74.9% at one year and 69.8% at two years, while the limb salvage rate was 84.2% and 74.7%, respectively. Conversely, the survival rate was only 71.6% at one year and 53.3% at two years, which was worse than both the patency rate and the limb salvage rate.

Based on the results of the Basil study, selection of EVT or surgical bypass depends on whether an autologous vein is available and if the patient has a life expectancy of at least two years. Although it is difficult to predict the life expectancy in a real-world clinical situation, our retrospective study of patients treated by surgical bypass or EVT[9] showed that 1) age ≥75 years, 2) serum albumin ≤3 g/dL, and 3) left ventricular ejection fraction ≤50% were predictors of a two-year life expectancy. Stratified analysis showed that the two-year mortality rate was 20% in patients without risks versus 70% in those with all of the risks. HD patients often have several risk factors; accordingly, their prognosis is poor.

Performing a clinical trial by randomly assigning patients to EVT or surgical bypass is extremely difficult in a real-world situation, and the number of such investigations has been quite limited after the Basil study. A study comparing EVT and surgical bypass was performed in Japan that assessed various patient characteristics by propensity score analysis,[10] revealing no differences between EVT and bypass with regard to three-year clinical outcomes in patients with CLI. The amputation-free survival rate was 66.3% vs. 62.0% ($p=0.44$), the limb salvage rate was 88.8% vs. 84.8% ($p=0.44$), the survival rate was 73.8% vs. 68.8% ($p=0.61$), and the freedom from adverse limb events rate was 61.3% vs. 69.1% ($p=0.27$) for EVT vs. bypass. Another study that used propensity score

matching to compare EVT and bypass for HD patients showed no differences in three-year results for overall survival (52% vs. 53%, p=0.96), major amputation (14% vs. 25%, p=0.71), and major adverse limb events (58% vs. 42%, p=0.63).[11] It is thought that the progress in EVT techniques and improved wound management have reduced the differences in clinical outcomes between EVT and bypass.

A subanalysis of the Registry of First-line Treatments in Patients With Critical Limb Ischemia (CRITISCH) in Germany compared perioperative results between patients who had CLI with end-stage renal failure and patients who had CLI with normal renal function.[12] This research was mainly conducted at institutions with a vascular surgery department in Germany and showed a significantly higher rate of EVT than surgical bypass as the first-line treatment (p=0.016). Among patients with CLI, 48% of those with normal renal function underwent EVT and 27% had surgical bypass as the first-line treatment, whereas 64% of patients with end-stage renal failure underwent EVT and 13% received bypass as the first-line treatment. Other first-line treatments included patch plasty, conservative management, and primary amputation. Comparison of perioperative results showed higher rates of perioperative death, amputation, and hemodynamic failure in the CLI patients with end-stage renal failure compared to those with normal renal function. Final review of the revascularization method, considering both the short-term and long-term results, concluded that EVT is a realistic first-line treatment for patients with CLI and end-stage renal failure.

Cost-benefit analysis is also important because of recent difficulties with the health care budget. Considering the poor short-term and long-term amputation-free survival rates of HD patients, the validity of performing revascularization becomes an issue. Although the costs vary between countries, it has been reported that EVT is more cost-effective as the first-line treatment in patients with end-stage renal failure.[13]

In Japan, surgical bypass is often thought to be more appropriate than EVT when considering treatment options for vascular lesions and the condition of the ischemic limb. However, EVT may be more appropriate than bypass in many patients with a poor general condition because of the high risk of perioperative complications and the poor long-term prognosis. Deciding which treatment option is more appropriate should be done on a case-by-case basis, especially in HD patients with CLI.

Current and Future EVT

EVT is still challenging in HD patients with PAD because of the frequent presence of heavily calcified lesions. Crossing the lesion with a guidewire or device and achieving sufficient dilatation can be difficult because of severe calcification. However, development of new devices for EVT has been rapid and has overcome some of these difficulties. Wires with a higher tip load and a tapered tip have been developed, making it easier to transmit torque and penetrate hard tissue in lesions. A device such as the Crosser (BARD Peripheral Vascular, Inc., Tempe, AZ, USA) can be used in cases where it is difficult to advance a wire across the lesion. Of course, these devices cannot necessarily guarantee initial success and further improvements are required.

HD may affect the long-term results of EVT. For example, comparison of the EVT results for the superficial femoral artery between HD and non-HD patients[14] showed superior results for the non-HD patients than HD patients, with one-year patency rates of 89% versus 82%, respectively, while the four-year patency rates were 79% versus 48%, respectively. When EVT was carried out for single below-the-knee lesion,[15] there was no difference in procedural success between HD patients and non-HD patients. However, the rate of freedom from major adverse limb events or perioperative death in non-HD patients was 86% and 82% at one and four years, respectively, while it was significantly lower in HD patients at 78% and 70%, respectively (p=0.01).

In Japan, Viabahn stents (W. L. Gore & Associates, Inc., Flagstaff, AZ, USA) became available for the superficial femoral artery at the end of 2016, and a drug-eluting balloon will be available soon. In addition, trials of ablation devices for calcified lesions are ongoing. If these devices become available clinically, improvement in the prognosis of ischemic limbs may be expected in HD patients. However, almost all of the trials of these new devices have excluded HD patients; hence, we need be careful for clinical application.

Summary

We discussed revascularization strategies for chronic HD patients with PAD. More patients are on chronic HD in Japan than in most other countries, although such patients are increasing worldwide. We believe that substantial useful data can be provided in the future by performing research in Japan.

Disclosure Statement

All authors have no conflict of interest.

Author Contributions

Review conception: SO, OI

Writing: SO
Critical review and revision: all authors
Final approval of the article: all authors
Accountability for all aspects of the work: all authors

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