Introduction

In Taiwan, more than 85% of patients with end-stage renal disease undergo maintenance hemodialysis (HD). The native arteriovenous fistula (AVF) accounts for a prevalence of more than 80% of the vascular access in our patients. Some mechanical factors may affect the patency of hemodialysis vascular access, such as surgical skill, puncture technique and shear stress on the vascular endothelium. Several medical factors have also been identified to be associated with vascular access prognosis in HD patients, including stasis, hypercoagulability, endothelial cell injury, medications, red cell mass and genotype polymorphisms of transforming growth factor-β1 and methylene tetrahydrofolate reductase. According to our previous study, AVF failure was associated with a longer dinucleotide (GT)n repeat (n ≥ 30) in the promoter of the heme oxygenase-1 (HO-1) gene. Our recent study also demonstrated that far-infrared therapy, a noninvasive and convenient therapeutic modality, can improve access flow, inflammatory status and survival of the AVF in HD patients through both its thermal and non-thermal (endothelial-improving, anti-inflammatory, antiproliferative, antioxidative) effects by upregulating NF-E2-related factor-2-dependent HO-1 expression, leading to the inhibition of expression of E-selectin, vascular cell adhesion molecule-1, and intercellular adhesion molecule-1. [J Chin Med Assoc 2009;72(3): 109–116]

Key Words: far-infrared therapy, genotype polymorphism, heme oxygenase-1, hemodialysis, vascular access
study,\(^6\) which showed that the unassisted patency of vascular access at 6 months was significantly poorer in patients with \(Q_a < 500 \text{ mL/min}\) than in those with \(Q_a \geq 500 \text{ mL/min}\) (13.6% vs. 92.2%; \(p < 0.0001\)). In addition to access flow, some mechanical factors influence AVF patency, such as the surgical skill, the puncture technique, and the shear stress on the vascular endothelia.

**Medical Factors Contributing to Malfunction of HD Vascular Access**

As shown in Table 1, several medical factors have been identified to be associated with vascular access stenosis in HD patients, including stasis, hypercoagulability, endothelial cell injury, medications, and red cell mass.\(^7\)

**Stasis**

Any cause of lower blood flow may predispose the vascular access to stasis, which is an important component of Virchow’s triad.

**Hypotension**

Intradialytic hypotension is connected with intravascular blood volume, which is quite variable for each patient.\(^8\) Regardless of the cause of hypotension, it results in a reduction in access flow, making it more susceptible to thrombosis.

**Hypoalbuminemia**

Hypoalbuminemia is related to a higher rate of thrombosis in PTFE AVG,\(^9\) especially in malnourished patients as well as in cirrhatics.

**Compression**

Inappropriate compression of the vascular access after HD may be associated with excessive direct pressure applied by the patient or nursing staff on a vascular access or by accident during sleep.

**Hypercoagulable states**

**Antiphospholipid antibodies**

Antiphospholipid antibodies include lupus anticoagulant and anticardiolipin antibodies. ESRD patients in general have been shown to have an elevated amount of circulating antiphospholipid antibodies, and this amount increases even more for those patients on HD.\(^10\) Lupus anticoagulant was shown to be associated with access thrombosis,\(^11\) whereas anticardiolipin antibodies were associated with recurrent access thrombosis.\(^12\) However, prospective studies are needed to determine the association with vascular access thrombosis.

**Hyperhomocysteinemia**

The common risk factor for both deep venous thrombosis and atherosclerosis is homocysteine, which might cause endothelial dysfunction, leading to impaired thrombolytic capacity and vasodilation of vascular

**Table 1. Prognostic factors affecting patency of hemodialysis vascular access**

<table>
<thead>
<tr>
<th>Mechanical factors</th>
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<tr>
<td>Surgical skill</td>
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<td>Technique of puncture vascular access</td>
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<td>Shear stress on the vascular endothelia</td>
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<table>
<thead>
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<th>Medical factors</th>
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<tr>
<td>Stasis: hypotension, hypoalbuminemia, compression</td>
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<td>Hypercoagulable states: antiphospholipid antibodies, hyperhomocysteinemia, factor V leiden, lipoprotein(a)</td>
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<tr>
<td>Endothelial cell injury: preexisting intimal hyperplasia, TNF-(\alpha), oxidative stress, calcium phosphate deposition, activated platelets</td>
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<tr>
<td>Medications: ACEI ((\uparrow2^\circ) patency in AVF), CCB ((\uparrow1^\circ) patency in AVG), aspirin ((\uparrow2^\circ) patency in AVG), dipyridamole ((\uparrow\text{AVG}^\circ) patency), warfarin ((\downarrow1^\circ) patency in AVG)</td>
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<tr>
<td>Genotype polymorphisms with poor patency of AVF:</td>
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<tr>
<td>TGF-(\beta)1: high-producer haplotypes (+869/-915: TC/GG and TT/GG)</td>
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<tr>
<td>MTHFR: T allele of MTHFR C677T</td>
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<tr>
<td>HO-1: a longer length polymorphism with GT repeat number (\geq 30)</td>
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<td>Lower access flow: &lt;500 mL/min for AVF, &lt;600 mL/min for AVG</td>
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<tr>
<td>Others: higher RBC mass, less exercise, late referral, infection, DM, smoking</td>
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<tr>
<td>Physical therapy: far-infrared therapy</td>
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\(\text{TNF-}\alpha=\text{tumor necrosis factor-}\alpha; \ \text{ACEI}=\text{angiotensin-converting enzyme inhibitor}; \ \uparrow=\text{increased}; \ \downarrow=\text{decreased}; \ \text{AVF}=\text{arteriovenous fistula}; \ \text{CCB}=\text{calcium channel blocker}; \ \ast=\text{primary}; \ \text{AVG}=\text{arteriovenous graft}; \ \downarrow=\text{decreased}; \ \text{TGF}-\beta\text{I}=\text{transforming growth factor-}\beta\text{I}; \ \text{MTHFR}=\text{methylene tetrahydrofolate reductase}; \ \text{HO}-1=\text{heme oxygenase-}\text{I}; \ \text{RBC}=\text{red blood cell}; \ \text{DM}=\text{diabetes mellitus}.\)
endothelium, and increased vascular smooth muscle cell (VSMC) proliferation. Fukasawa et al showed that the genotype polymorphism responsible for hyperhomocysteinemia was associated with a higher risk of AVF thrombosis. Some studies could not demonstrate the relationship between hyperhomocysteinemia and vascular access thrombosis. A prospective study showed that hyperhomocysteinemia was associated with a 4% increased risk of vascular access failure. It was also shown that increased homocysteine levels could cause VSMC proliferation, while folic acid supplementation inhibited this homocysteine-induced proliferation. Treatment of hyperhomocysteinemia with oral folate has shown various results. Some studies observed that there was no significant effect of folate at doses of 1–5 mg/day, while others showed a significant decrease. Bostom et al showed that a daily 15 mg dose of folic acid could lower plasma homocysteine levels in only one third of patients. The best factor predicting response to folate is the baseline homocysteine levels, and higher doses of folate of 30–60 mg/day were only more effective than 15 mg/day in patients with the methylene tetrahydrofolate reductase (MTHFR) 677TT genotype. More studies are needed to identify whether decreasing homocysteine levels in HD patients can result in a significant reduction of vascular access thrombosis.

Factor V leiden
A mutation at nucleotide position 1691 of the factor V gene leads to the formation of factor V leiden, which was associated with peripheral vascular graft thrombosis due to hypercoagulability on account of resistance to activated protein C. Patients with homozygous mutation of the factor V gene have a higher risk of developing vascular access thrombosis than those with heterozygous mutation.

Lipoprotein(a)
Association of lipoprotein(a) with atherothrombotic complications was reported in both the general and ESRD populations but with equivocal results. It was shown to be a risk factor for thrombosis in either white or black patients, but the power in race-specific analyses was inadequate in both studies.

Endothelial cell injury
Many factors lead to endothelial cell injury or dysfunction and they are listed as follows.

Preexisting intimal hyperplasia
Preexisting intimal hyperplasia is an important cause of inadequate radial artery diameter, and histologic examination revealed that this is quite common in patients undergoing HD. Only diabetes and age are risk factors for preexisting intimal hyperplasia. Intimal hyperplasia of preexisting radial artery is also associated with a lower frequency of 1-year patency of AVFs.

Tumor necrosis factor-α (TNF-α)
Leukocytes release TNF-α, which could induce proliferation of vascular smooth muscles leading to subsequent intimal hyperplasia. The interaction between PTFE AVGs and circulating peripheral blood mononuclear cells located upstream of the venous anastomosis potentiates the release of TNF-α.

Oxidative stress
Oxidative hyperactivity in the uremic status usually leads to an increased amount of circulating and tissue inflammatory molecules. Interaction with dialysis membranes have also been reported as an important cause leading to oxidative stress, resulting in an increased expression of endothelin-1, which has been associated with intimal hyperplasia and smooth muscle cell vasoconstriction. Transforming growth factor-β and platelet-derived growth factor have also been implicated in intimal hyperplasia but seem to be clustered at the venous end of the failed AV access.

Calcium phosphate deposition
Stenosis of AVFs were associated with calcium phosphate deposition, which is mainly in the form of calcium apatite. Brushite, another calcium phosphate precipitate, may be formed under acidic conditions and be found in stenotic AVFs, but it was not present in nonstenotic AVFs and normal veins (non-AVF). More studies are needed to identify whether brushite is the cause or a result of vascular access dysfunction.

Activated platelets
Injury to endothelial cells exposes the basement membrane and extracellular matrix leading to activation of platelets. It has been shown that higher levels of circulating activated platelets are associated with shorter survival of AV access. Inhibition of platelet activation with aspirin and sulfinpyrazone has been shown to prevent recurrent access thrombosis.

Medications
The largest study evaluating the effects of specific medications on AV access patency is the Dialysis Outcomes and Practice Patterns Study (DOPPS). This prospective, international study observed 900 AVFs and 1,944 AVGs, and excluded failure of AV accesses within 30 days due to technical failure. There were
some informative results. The primary patency of AVFs was not improved by any drug, and only angiotensin-converting enzyme inhibitors improved secondary patency. Calcium channel blockers improved primary patency of AVGs, and aspirin improved secondary patency. Warfarin reduced primary graft patency, although this may be due to deficiency of protein C or S. Another study showed that dipyridamole alone was associated with a significant risk reduction for AVG thrombosis, while aspirin did not improve the risk of thrombosis. In addition, calcium channel blockers have been shown to inhibit neointimal hyperplasia in AVGs.

Red blood cell mass
According to the report by the Canadian Erythropoietin Group, the incidence of vascular access thrombosis was significantly increased in those patients receiving erythropoietin. Churchill et al showed that erythropoietin was not related to access thrombosis; however, their study was not double-blinded. More double-blinded, placebo-controlled, randomized trials are needed to determine the role of erythropoietin in AV access patency.

Exercise
Leaf et al reported that an isometric exercise training program could increase the diameter of the cephalic vein, theoretically increasing the possibility of creation of an AVF. More studies are needed to evaluate the effect of exercise on patency rates.

Timely referral
Timely referral to nephrologists enables more precise prediction of the appropriate timing for the placement of a fistula or graft and the initiation of dialysis, which could help HD patients avoid implantation of any temporary catheter access. Not only would this avoid the complications related to catheter placement, but it would also reduce the frequency of AV access failure. Chesser and Baker reported that early referral to a nephrologist was associated with a higher frequency of patients starting HD on a functioning AVF and lower overall mortality.

Infection
About 50% of vascular access infections are caused by Staphylococcus epidermidis, with Gram-negative organisms accounting for approximately 23%. Staphylococcus aureus accounts for about 20% of infections, and is more likely than S. epidermidis to lead to bacteremia. In addition, sources of bacterial seeding to AVGs may come from sites other than dialysis punctures, such as infective endocarditis, intravenous route used by drug abuser or intra-abdominal abscess.

Cardiovascular risk factors
Certain demographic characteristics have been implicated in AV access failure. Smoking, a risk factor for atherosclerosis in general, is associated with both early and late fistula failure. Diabetes has also consistently been associated with access failure in prospective studies, possibly due to an increase in VSMC proliferation.

Genotype Polymorphisms and AVF Malfunction
Transforming growth factor-β1 (TGF-β1)
The pathologic features of vascular access stenosis are composed of intimal hyperplasia, VSMC proliferation in the media with subsequent migration to intima, and excessive accumulation of extracellular matrix, which are mediated by several growth factors such as TGF-β1. The synthesis of TGF-β1 interindividually differs due to the 2 single nucleotide polymorphisms in the DNA sequence encoding the signal sequence of the TGF-β1 protein, located at position +869 (codon 10, T>C, leucin>proline) and position +915 (codon 25, G>C, arginine>proline). Three different cytokine-producer types are distinguished: high-producer haplotypes are TC (codon 10)/GG (codon 25) and TT/GG; intermediate-producer haplotypes are CC/GG, TC/GC, and TT/GC; and low-producer haplotypes are CC/CC, CC/GC, TT/CC, and TC/CC, respectively. AVF patency was significantly associated with the TGF-β1 genotype; patencies were 62.4% and 81.2% after 12 months for TGF-β1 high and intermediate producers, respectively.

MTHFR
The MTHFR C677T polymorphism has been reported to be closely related to plasma homocysteine level. Percentages of patients who experienced AVF malfunction were as follows: CC (12.6%), CT (20.3%), and TT (31.8%). The number of those who experienced obstruction was significantly larger with TT than CC \((p<0.01)\). The odds ratio of genetic polymorphisms predicting AVF malfunction is 1.77 for T allele-containing genotypes of MTHFR.15

Heme oxygenase-1 (HO-1)
HO-1 is another factor associated with higher risk of developing some vascular diseases. HO plays a crucial role in controlling intracellular heme levels by catalyzing the rate-limiting step in the metabolism of heme. HO cleaves the α-meso carbon bridge of heme, producing equimolar quantities of carbon monoxide (CO),
biliverdin, and free iron. Biliverdin is subsequently metabolized to bilirubin by biliverdin reductase, and free iron is promptly sequestered by ferritin. There are 3 distinct isoenzymes of HO (HO-1, HO-2, HO-3). HO-1 is an inducible 32-kDa protein that is ubiquitously distributed and is located at chromosome 22q12. HO-1 induction stimulates cell cycle progression and proliferation in vascular endothelium, but inhibits the growth of VSMCs via the release of CO. The mechanisms of CO-mediated apoptosis in VSMCs include: (1) increase of p53 expression, which is a proapoptotic protein; (2) release of cytochrome c from the mitochondria; and (3) release of biliverdin and bilirubin, which at high concentrations are known inducers of apoptosis.

Length polymorphisms in the dinucleotide GT repeats
A (GT)n dinucleotide repeat with various length was identified in the proximal promoter region. It functions as a negative regulatory region and is located between −198 and −258 of the human HO-1 promoter. Individuals with shorter repeats (≤ 25) demonstrate higher levels of HO-1, whereas individuals with longer repeats (> 25) have lower levels of HO-1.

HO-1 length polymorphisms and cardiovascular diseases
Length polymorphisms of GT repeat in the promoter region of the HO-1 gene vary between subjects and correlate with disease activity. It was reported that a longer length polymorphism of GT repeat (> 25 or 27 or 30) in HO-1 promoter was associated with susceptibility to the following conditions: restenosis and increased vascular inflammation after percutaneous transluminal angioplasty, coronary artery disease in type 2 diabetic patients, Japanese patients with coronary risk factors, and abdominal aortic aneurysms.

Long GT repeat in HO-1 promoter and poor AVF patency (Figure 1)
In our study, 603 HD patients were enrolled; 178 had history of AVF failure, while 425 did not. After correction for many factors (such as age, sex, HD duration, underlying cause of ESRD), a significantly higher frequency of AVF failure was still noted for the L/L and L/S genotypes of HO-1, with a hazard ratio of 2.040 when compared with the S/S genotype. The proportion of AVF failure increased from 20.3% for the S/S genotype to 31.0% for the L/S genotype and 35.4% for the L/L genotype. The unassisted patencies of AVF at 5 years decreased significantly from 83.8% to 75.1% and 69% in S/S, L/S and L/L genotypes, respectively.

Far-infrared Therapy Improves AVF Patency Through Upregulation of HO-1 Expression (Figure 1)

Introduction
Infrared radiation is an invisible electromagnetic wave with a longer wavelength than that of visible light. According to the difference in wavelength, infrared radiation can be divided into 3 categories: near-infrared radiation (0.8–1.5 μm); middle-infrared radiation (1.5–5.6 μm); and far-infrared (FIR) radiation (5.6–1,000 μm). Infrared radiation transfers energy that is perceived as heat by thermoreceptors in the skin.

Clinical applications
The application of FIR radiation includes food preservation and health promotion. Animal studies have demonstrated that FIR improves skin blood flow, leading to the use of FIR in the treatment of ischemic lesions and necrosis of skin tissue due to trauma, diabetes mellitus and peripheral arterial-occlusive disease. In addition, some studies indicate that FIR therapy may improve endothelial function and reduce the frequency of some cardiovascular diseases, including improving endothelial dysfunction in patients with coronary risk factors, heart failure and arrhythmia.

FIR therapy improves access flow and unassisted patency of AVF in HD patients (Figure 1)
In our previous study, a total of 145 HD patients were enrolled, with 73 in the control group and 72 in the FIR group. The Qa1/Qa2 and Qa3/Qa4 were
defined as the Qa measured at the beginning, at 40 minutes later in the HD session prior to the initiation, and at the end of the study, respectively. The incremental change in Qa in the single HD session with FIR therapy was significantly higher than in that without FIR therapy (13.2 ± 114.7 mL/min vs. −33.4 ± 132.3 mL/min). Compared with controls, patients receiving FIR therapy for a year had: (1) lower incidence (12.5% vs. 30.1%) of AVF dysfunction; (2) higher values of incremental change in access flow; and (3) better unassisted patency of AVF (85.9% vs. 67.6%).

**Mechanisms of FIR therapy**

Our results indicate that both short-term and long-term FIR can increase access flow. Moreover, there is an additive benefit of both short- and long-term effects. The short-term thermal effect of FIR results in vasodilatation and increasing Qa. According to the report by Hartel et al, the temperature can be increased up to 4°C in 10 mm depth of tissue. In addition, infrared therapy may allow multiple energy transfers as deep as 2–3 cm into subcutaneous tissue without irritating or overheating the skin like unfiltered heat radiation. The skin temperature steadily increased to a plateau around 38–39°C during FIR treatment for 30–60 minutes as long as the distance between the ceramic plate and the skin was more than 20 cm.

In addition to the short-term thermal effect, the increase in both Qa and fistula patency in this study may result from the long-term (accumulated thermal and non-thermal) effect of FIR therapy. In particular, FIR may improve endothelial function, which was observed not only in animal studies but also in one clinical study. Yu et al suggest that the beneficial effect of FIR therapy on skin blood flow may be related to L-arginine/nitric oxide pathway. Akasaki et al found that repeated FIR therapy could upregulate eNOS expression and augment angiogenesis in an apolipoprotein E-deficient mouse model of unilateral hind limb ischemia. Moreover, Ikeda et al reported that 4 weeks of sauna therapy significantly increased serum nitrate concentrations as well as the expression of mRNA and protein of eNOS in the aortas of TO-2 hamsters. In addition, Imamura et al showed that 2 weeks of repeated sauna therapy significantly improved vascular endothelial function, resulting in an increase in flow-mediated endothelium-dependent dilatation of the brachial artery from 4% to 5.8% in patients with coronary risk factors.

Our recent study also showed that FIR induced expression of HO-1 via stimulating NF-E2-related factor-2 (Nrf2)-dependent promoter activity, with the maximal time-course effect on the expression of HO-1 and Nrf2 both at 6 hours. Tumor necrosis factor-α (TNF-α)-induced expression of E-selectin, vascular cell adhesion molecule-1 (VCAM-1), and intercellular cell adhesion molecule-1 (ICAM-1) were maximally suppressed by FIR therapy at 4, 6 and 24 hours, respectively. Higher expression of HO-1 may explain the antiproliferative and anti-inflammatory effect of FIR therapy.

Besides activating expression of eNOS and HO-1, inhibiting neointimal hyperplasia and decreasing oxidative stress are 2 other non-thermal effects of FIR therapy. Kipshidze et al found that nonablative infrared laser therapy inhibited neointimal hyperplasia after PTCA in cholesterol-fed rabbits for up to 60 days due to suppression of the growth of VSMCs. In addition, Masuda et al showed that patients receiving FIR dry sauna for 45 minutes a day for 2 weeks had lower systolic blood pressure and urinary levels of 8-epi-prostaglandin F2α, which is a chemically stable product of lipid peroxidation, and the level has been suggested to be a reliable marker of oxidative stress in vivo.

In conclusion, many factors may affect the prognosis of vascular access. FIR therapy, a noninvasive and convenient therapeutic modality, can improve Qa, inflammatory status and survival of the AVF in HD patients through both its thermal and the above-mentioned non-thermal (anti-inflammatory) effects by upregulating Nrf2-dependent HO-1 expression, leading to the inhibition of E-selectin, VCAM-1 and ICAM-1 expression.

**References**