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Administration of a High-Dose Erythropoietin-Stimulating Agent in Hemodialysis Patients is Associated with Late Arteriovenous Fistula Failure

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Purpose: Investigating the risk of vascular access failure is critical for maintenance hemodialysis (MHD) patients. Erythropoietin stimulating agents (ESA) typically used for anemia of chronic kidney disease (CKD) may also stimulate neointimal hyperplasia, which is the most important factor in late arteriovenous fistula (AVF) failure. The aim of this study was to investigate whether ESA treatment is associated with late AVF failure.

Materials and Methods: The late AVF failure group comprised 51 patients who underwent percutaneous intervention or surgery for fistula revision after successful use for at least three months. There were 51 controls whose AVF had been patent for at least 24 months.

Results: The mean time from the first cannulation to late loss of AVF patency was 8.4±4.2 months. The average weekly dose of ESA was significantly higher in patients with AVF failure (4782.2±2360.5 IU/mL/wk vs. 7161.8±2775.2 IU/mL/wk, $p<0.001$). The only independent predictor of late AVF failure in multivariate analysis was high average ESA dose (odds ratio=1.015, 95% confidence interval=1.002–1.028, $p=0.022$).

Conclusion: Patients with late AVF patency loss exhibit an association with a higher dose of ESA, although causality is unproven. Further study to elucidate potential mechanisms is warranted.

Key Words: Arteriovenous fistula, chronic kidney disease, erythropoietin stimulating agents, maintenance hemodialysis, neointimal hyperplasia

INTRODUCTION

It is critical that patients undergoing chronic hemodialysis maintain vascular access without failure. Autologous arteriovenous fistula (AVF) is the preferred hemodialysis access due to its many advantages, including greater duration in function and lower infection rate compared with arteriovenous grafts (AVG) and central venous hemodialysis catheters.[1,2] However, mature AVFs are still at risk of malfunction, as they require repeated intervention to maintain patency and commonly necessitate subsequent vascular access.[3] Late AVF failure is generally defined as failure occurring after three months of use.[4] Neointimal hyperplasia is thought to be the most important factor causing late loss of AVF patency after a period of successful use.[3,5] The mechanism by which neointimal hyperplasia progresses and stenosis and/or thrombosis develop during chronic hemodialysis treatment is unclear, but is presumably due to a combination of shear stresses, repeated needle injury, and uremic milieu.[3,5,6]

Erythropoietin stimulating agents (ESA) are used in the treat-

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ment of anemia in patients with chronic kidney disease (CKD), but it has some adverse effects, such as hypertension and cardiovascular and cerebrovascular events.[7] Interestingly, several experimental studies have shown that ESA could stimulate vascular smooth muscle cells[8] and induce neointimal hyperplasia.[9] However, the role of ESA in the process of late AVF loss in patients on chronic hemodialysis is still inconclusive.[10] The aim of the present study was to determine whether ESA treatment is associated with late loss of AVF function after successful maturation in patients receiving chronic hemodialysis.

MATERIALS AND METHODS

Patients

This was a retrospective case-control study of patients who received maintenance hemodialysis (MHD) and underwent AVF creation. All patients had end stage renal disease (ESRD) and were treated with MHD at the CHA Bundang Medical Center hemodialysis center between 2006 and 2015. We selected patients who received percutaneous intervention or surgery to revise their fistula after successful use of AVF for at least three months to be enrolled in the late AVF failure group. In the percutaneous intervention, vessels were dilated using a balloon catheter [Armada™ 35 (Abbott Vascular, Santa Clara, CA, USA), MUSTANG™ (Boston Scientific Co., Marlborough, MA, USA)] with a diameter varying from 4–8 mm. The balloon was inflated for 30–60 seconds and repeated as necessary. Balloon inflation pressure was 14–24 atm as recommended by the manufacturer.

Vascular access failure events occurred in 195 patients during that time period. Among those patients, 68 had an AVG. Only 51 patients were ultimately included in the late AVF failure group (Fig. 1). Fifty-one controls were selected from our centers whose AVF had been patent without an episode of access failure for at least 24 months. Neither cases nor controls had a history of cancer, coagulation disorder, active infection, or AVG with synthetic material. AVF operations were performed within one month after the first MHD in both groups. All patients initiated AVF cannulation within 3 months after AVF formation. All patients were undergoing chronic bicarbonate hemodialysis for a mean time of 4.0 hours, three times a week. The blood flow rate ranged between 250 and 300 mL/min, whereas a dialysate flow rate of 500 mL/min was routinely used. Kt/V was evaluated monthly as a marker of dialysis efficiency. The study was approved by the Institutional Review Board of the CHA Bundang Medical Center, CHA University. Because the study involved the analysis of data already collected and the data had individual identifying information removed, the ethics board waived the need for individual patient consent.

Clinical variables

Patient demographic, clinical, and vascular access data, including age, gender, and etiology of ESRD (e.g., diabetes, hypertension, glomerulonephritis, polycystic kidney disease, or unknown), AVF site (forearm or upper arm), medications (antihypertensive drugs, antiplatelet agents, calcium containing ag-

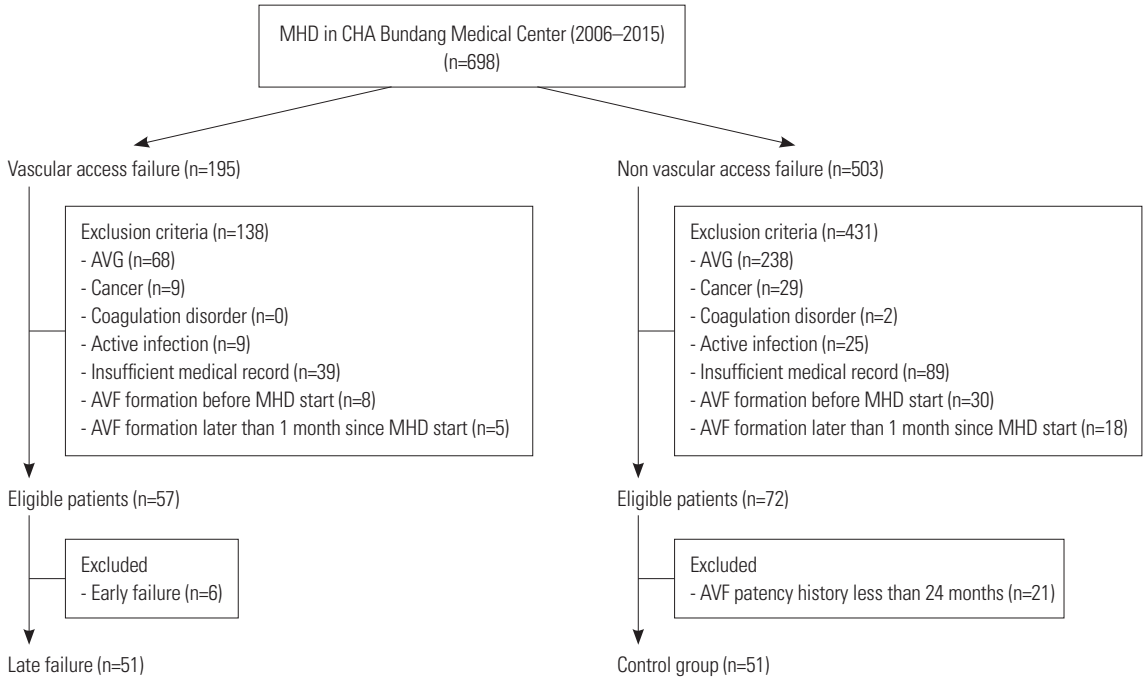

Fig. 1. Flow chart illustrating study population enrollment. A total of 1625 patients received MHD at the hemodialysis center of CHA Bundang Medical Center between 2006 and 2015. Vascular access failure events occurred in 245 patients. After applying exclusion criteria, only 51 patients were eligible for the late AVF failure group. AVG, arteriovenous graft; AVF, arteriovenous fistula; MHD, maintenance hemodialysis.

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ents, or vitamin D analogues), heparin dose, and other comorbidities (ischemic heart disease, cerebrovascular disease, or peripheral vascular disease), were obtained by medical record review. Cardiovascular diseases were defined when patients had any medical history of angina pectoris, positive treadmill test, myocardial infarction, percutaneous transluminal coronary angioplasty, coronary artery bypass surgery, or congestive heart failure. Cerebrovascular diseases were defined when patients had any medical history of stroke, transient ischemic attack, or intracranial hemorrhage. The combined cardiovascular disease group included patients who had cardiovascular and cerebrovascular disease. Laboratory findings were collected, including serum hemoglobin, serum calcium, blood urea nitrogen, phosphate, intact parathyroid hormone (iPTH), uric acid, total cholesterol, low density lipid cholesterol, c-reactive protein (CRP), 25-hydroxyvitamin D, and albumin, at the time of the first access cannulation. The mean weekly erythropoietin doses and the mean hemoglobin level were calculated using medical records through the period from the first AVF use to an event or at least two years after the first AVF cannulation for the control group. For dose conversion, 1 mcg of darbepoetin alpha was converted to 200 IU epoetin alpha.[11] Blood flow rate data were collected for the three most recent hemodialysis treatments for controls or for the last three hemodialysis treatments before late AVF failure for cases. Loss of AVF patency due to thrombosis was defined as the need for percutaneous intervention, thrombectomy, or reconstruction surgery to revise the fistula.

Statistical analysis

Categorical variables were recorded as numbers and percentages. Continuous variables were presented as the mean±standard deviation. Student's t-test and the Mann-Whitney U test were used to compare continuous variables. Categorical vari-

Table 1. Baseline Characteristics of the Study Population

Characteristics	Overall (n=102)	No AVF failure (n=51)	AVF failure (n=51)	*p* value
Male, n (%)	63 (61.7)	31 (60.7)	32 (62.7)	0.839
Age (yr)	54.2±13.5	50.6±13.4	57.9±12.7	0.006
BMI (kg/m^2)	22.7±3.03	23.0±3.35	22.3±2.6	0.275
MBP (mm Hg)	97.7±13.7	98.1±14.8	97.4±12.7	0.803
First needling time (month)	2.34±0.48	2.27±0.45	2.41±0.50	0.147
HTN, n (%)	84 (82.3)	38 (74.5)	46 (90.1)	0.038
Diabetes, n (%)	64 (62.7)	23 (45.0)	41 (80.3)	<0.001
Cardiovascular disease, n (%)	15 (14.7)	2 (3.9)	13 (25.4)	0.002
Cerebrovascular, n (%)	9 (8.8)	2 (3.9)	7 (13.7)	0.160
Combined CVD group, n (%)	21 (20.5)	4 (7.8)	17 (33.3)	0.001
Heparin, loading (IU/mL)	1039.2±376.8	1039.2±372.0	1039.2±385.2	1.000
Heparin, continuous (IU/mL)	300.9±179.6	270.5±172.0	331.3±183.5	0.088
Blood flow rate (mL/min)	264.8±34.6	271.5±27.5	258.0±39.5	0.048
Forearm fistula, n (%)	90 (88.2)	46 (90.1)	44 (86.2)	0.539
Hemoglobin (g/dL)	9.3±1.5	9.4±1.5	9.3±1.5	0.842
Albumin (mg/dL)	3.4±0.6	3.6±0.5	3.2±0.6	0.001
Uric acid	7.8±1.9	7.8±2.0	7.8±1.8	0.959
BUN (mg/dL)	22.7±3.03	66.2±33.2	67.5±22.5	0.811
Creatinine (mg/dL)	7.9±3.5	8.5±4.0	7.4±2.8	0.093
Calcium (mg/dL)	8.1±0.9	8.2±0.9	8.0±1.0	0.309
Phosphate (mg/dL)	5.0±1.6	5.1±1.6	4.9±1.6	0.456
iPTH, mg/dL (IQR)	142.9 (69.4–221.9)	157.7 (83.0–363.3)	119.7 (55.4–180.8)	0.017
T. cholesterol (ug/dL)	155.5±44.9	157.4±35.0	153.6±53.2	0.676
LDL cholesterol (mg/dL)	86.0±39.1	87.1±37.7	85.0±40.8	0.786
CRP, mg/dL (IQR)	0.2 (0.1–0.7)	0.2 (0.1–0.5)	0.3 (0.1–1.6)	0.059
25-OH Vitamin D3 (ug/mL)	14.4±8.7	15.5±8.3	12.7±9.2	0.340
spKT/V	1.4±0.2	1.4±0.1	1.3±0.3	0.254
ESA (IU/mL/wk)	5972.0±2828.6	4782.2±2360.5	7161.8±2775.2	<0.001
ESA (IU/mL/wk/kg)	99.4±50.0	79.2±42.4	119.6±49.2	<0.001

AVF, arteriovenous fistula; BMI, body mass index; BUN, blood urea nitrogen; CRP, C-reactive protein; Combined CVD group, combined cardiovascular or cerebrovascular disease group; ESA, erythropoietin stimulating agent; First needling time, first needling time since AVF formation; HTN, hypertension; LDL, low density lipid; MBP, mean blood pressure; iPTH, intact parathyroid hormone; T. cholesterol, total cholesterol; 25-OH Vitamin D3, 25 hydroxy vitamin D.
Data are expressed as the mean±standard deviation, median (IQR) or the count (percentage).

ables were compared using the χ^2 test or Fisher's exact test. Binary logistic regression analysis was performed to investigate the effects of covariates on AVF patency. All *p*-values<0.050 were considered significant. Statistical analyses were performed using SPSS for Windows (version 21; SPSS Inc., Chicago, IL, USA).

RESULTS

Study population

Clinical and biochemical characteristics are shown in Table 1. The mean age of the study population was 54.2±13.5 years, and men comprised 61.7% of the population. The etiologies of ESRD were diabetic nephropathy (62.7%), hypertension (21.5%), glomerulonephritis (5.8%), autosomal dominant polycystic kidney disease (1.9%), and unknown (7.8%). Most patients had radiocephalic fistulas in the forearm (88.2%). The mean initial dose of heparin was 1039.2±376.8 IU/mL, and the maintenance dose was 300.9±179.6 IU/mL/hr. The mean ESA dose was 5972.0±2828.6 IU/mL/wk and 99.4±50.0 IU/mL/wk/kg (Table 1).

Clinical characteristics of patients with late AVF failure

The mean duration of MHD was 59.7±32.2 months in the control group and 11.8±4.2 months in the late AVF failure group. The mean time from the first cannulation to late loss of AVF patency was 8.4±4.2 months.

Among the 51 eligible late AVF failure patients, most AVF stenoses were located in the proximal draining vein. The stenotic sites in 23 patients were in the proximal draining veins, and the sites in 20 patients were near both anastomosis sites and the proximal draining veins. Of these patients, one opted to abandon the original access site and underwent double lumen catheter insertion, and two underwent a thrombectomy. The remaining 48 patients underwent percutaneous angioplasty, of which all were successful.

Baseline demographics and comorbidities of patients who developed late loss of functional AVF patency were compared with patients without AVF failure in Table 1. Patients with late AVF failure were significantly older and more likely to have comorbid conditions, such as hypertension, diabetes mellitus, and cardiovascular disease. Additionally, patients with late AVF failure had significantly lower serum albumin and iPTH levels, compared to patients without late AVF failure. Blood flow rates during MHD treatment were significantly lower in the group with late AVF failure. Most importantly, the average weekly dose of ESA was significantly higher in the patients with late loss of functional AVF patency (4782.2±2360.5 IU/mL/wk vs. 7161.8±2775.2 IU/mL/wk, $p<0.001$ and 79.2±42.4 IU/mL/wk/kg vs. 119.6±49.2 IU/mL/wk/kg, $p<0.001$) (Table 1, Fig. 2). Serum hemoglobin levels, however, were not different between groups. We also compared mean hemoglobin levels between groups during the period from the first AVF use to an event or at least two years since the first AVF cannulation for the control group. The mean hemoglobin level was slightly higher in the AVF failure group, although the difference was not statistically significant (9.6±0.5 g/dL vs. 9.5±1.5 g/dL, $p=0.728$) (Fig. 3).

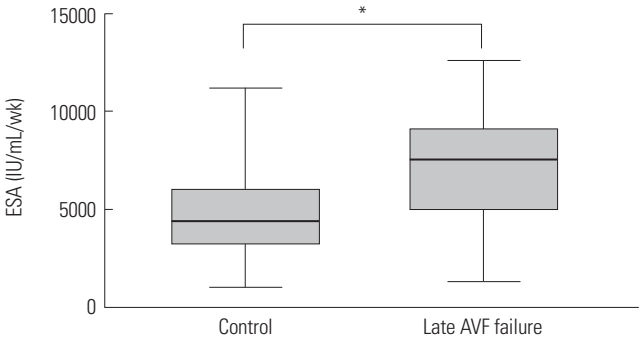

Fig. 2. Mean ESA dose according to AVF patency loss. The mean ESA dose was 7161.8±2775.2 IU/mL/wk for the AVF failure group and 4782.2±2360.5 IU/mL/wk for the control group. The difference in mean ESA dose between the two groups was statistically significant (*$p<0.001$). AVF, arteriovenous fistula; ESA, erythropoietin stimulating agent.

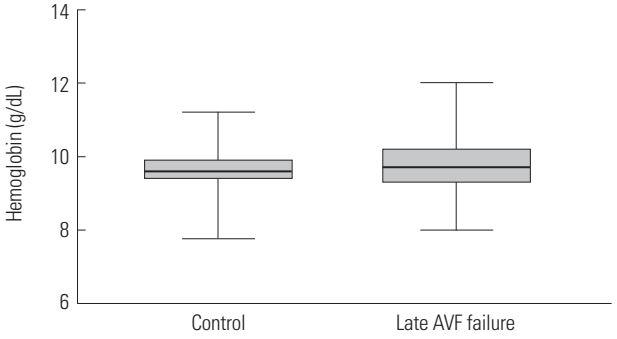

Fig. 3. Mean hemoglobin level according to AVF patency loss. The mean hemoglobin level was 9.6±0.5 g/dL in the AVF failure group and 9.5±1.5 g/dL in the control group. The mean hemoglobin level was slightly higher in the AVF failure group, but the difference was not statistically significant ($p=0.728$). AVF, arteriovenous fistula.

No differences in sex, access location, or medications were observed between those with and without late failure (Table 1 and 2).

Multivariate analysis

Binary logistic regression analysis was performed to assess the effects of covariates on AVF patency (Table 3). We used the continuous value of ESA in IU/mL/wk/kg to evaluate the effect of ESA dose. The variables chosen for inclusion in the multivariable logistic regression analysis were those found to be significantly correlated with late loss of functional patency on univariate analysis. Variables that met this criterion were age; presence of diabetes, hypertension, or ischemic heart disease; blood flow rate; serum albumin; iPTH; and dose of ESA. The only independent predictor of late loss of AVF patency in multivariate analysis was a high average ESA dose (odds ratio=1.015, 95% confidence interval=1.002–1.028, $p=0.022$) (Table 3).

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Table 2. Medications Taken by the Study Population

Medication	Overall (n=102)	No AVF failure (n=51)	AVF failure (n=51)	*p* value
ACEi/ARB, n (%)	82 (80.3)	40 (78.4)	42 (82.3)	0.618
Beta blocker, n (%)	40 (39.2)	20 (39.2)	20 (39.2)	1.000
Calcium channel blocker, n (%)	69 (67.6)	33 (64.7)	36 (70.5)	0.525
Aspirin, n (%)	49 (48.0)	20 (39.2)	29 (56.8)	0.074
Clopidogrel, n (%)	13 (12.7)	5 (9.8)	8 (15.6)	0.394
Cilostazol, n (%)	4 (3.9)	2 (3.9)	2 (3.9)	1.000
Calcium, n (%)	71 (69.6)	40 (78.4)	31 (60.7)	0.053
Vitamin D, n (%)	15 (14.7)	8 (15.6)	7 (13.7)	0.780

ACEi/ARB, angiotensin converting enzyme inhibitor/angiotensin receptor blocker; AVF, arteriovenous fistula.

Table 3. Binary Logistic Regression Analysis for AVF Failure

	Univariate model		Multivariate model	
	Odds ratio (95% CI)	*p* value	Odds ratio (95% CI)	*p* value
ESA dose (IU/mL/kg)	1.020 (1.010–1.031)	<0.001	1.015 (1.002–1.028)	0.022
Age	1.044 (1.011–1.078)	0.008	1.028 (0.982–1.076)	0.233
HTN	0.318 (0.104–0.971)	0.044	0.830 (1.195–3.531)	0.800
Diabetes	0.200 (0.083–0.485)	<0.001	0.423 (0.144–1.244)	0.118
Cardiovascular disease	0.119 (0.025–0.561)	0.007	0.297 (0.055–1.597)	0.157
Blood flow rate	0.988 (0.975–1.000)	0.050	0.989 (0.974–1.003)	0.128
Albumin	0.310 (0.149–0.646)	0.002	0.685 (0.283–1.658)	0.410
iPTH	0.996 (0.993–0.999)	0.020	0.997 (0.993–1.001)	0.123

AVF, arteriovenous fistula; CI, confidence interval; ESA, erythropoietin stimulating agent; HTN, hypertension; iPTH, intact parathyroid hormone.

DISCUSSION

In this study, we retrospectively compared 51 cases and controls. All of them had successfully matured AVF and had used it for vascular access for more than three months. We compared the mean weekly ESA dose between the AVF patency loss group and controls, and we also compared the mean hemoglobin levels during the study period. This study showed that high-dose ESA could be a risk factor for late AVF patency loss. Notably, there was a significant relationship between ESA dosage and late AVF patency failure on multivariate analysis.

Traditionally, it is well known that ESA resistance is associated with nutritional or inflammation status, which can be associated with low albumin or high CRP levels. Such patients would continuously need a higher ESA dose in order to maintain an appropriate hemoglobin level.[12,13] In our study, the albumin level was significantly lower and CRP was not significantly higher in the AVF failure group. Furthermore, patients in the AVF failure group were older and had more co-morbidities. However, these factors were not statistically significant in multivariate analysis, which could suggest that the high ESA dose in the AVF fistula group was not influenced by ESA resistance as a confounding factor. Although age and diabetes are known to be significant factors for various disease states,[14] the effects of age or diabetes on AVF patency are still controversial.[15-17] In our study, patients with late AVF failure were significantly older and more likely have diabetes than the patients with patent AVF in univariate analysis. However these differences were no longer significant in multivariate analysis.

Studies exploring the relationship between ESA treatment and AVF failure are scarce. Grandaliano, et al.[18] reported that the weekly ESA dose was higher in a group of patients with AVF failure than patients without in their five-year case-control study. However, they did not mention the exact duration between AVF formation and event and did not consider the effects of medications, such as antiplatelet agents or antihypertensive drugs. Another study conducted by Roozbeh, et al.[19] suggested that ESA administration influenced fistula patency (RR=10.92, p=0.021), but did not compare to controls or calculate the exact ESA dose. A three-year prospective study with 16 ESA-treated and 14 placebo-treated patients undergoing chronic hemodialysis showed that ESA therapy had no effect on the risk of progressive stenosis of native AVF.[10]

There are several possible mechanisms underlying the use of ESA leading to late failure of native AVF. First, the growth index of vascular smooth muscle cells from spontaneously hypertensive rats is reportedly enhanced by ESA treatments.[20] Accelerated smooth muscle cell-rich neointimal hyperplasia induced by ESA has been observed in mice.[9]

Second, increased hemoglobin concentration can mediate increased plasma viscosity and elevated red blood cell aggregation can limit microcirculatory flow.[21,22] The rapidity of the increase in hemoglobin concentration could exacerbate the cardiovascular risk through a hemodynamic or rheologic mechanism. The Normal Hematocrit Study and the CHOIR trial[23] reported the relationship between excessive rates of hemoglo-

bin increase and the risk of adverse cardiovascular outcomes.[24]

The third possibility is an increased platelet count or reactivity. Several previous studies have reported that ESA therapy could decrease bleeding time in CKD patients on dialysis.[25,26] One study in dogs suggested that ESA promotes the production of reticulated platelets and that these newly synthesized platelets are more reactive, compared with controls.[27] In a randomized controlled trial, Stohlawetz, et al.[28] enrolled healthy human volunteers and found that ESA markedly enhanced platelet reactivity. In uremic patients, ESA therapy increased circulating hematopoietic progenitor cells[29] and increased platelet aggregation.[30]

Other possible mechanisms are ESA-induced hypertension or impaired vasodilation.[31-33] Increased viscosity and enhanced vascular reactivity by the correction of hypoxia due to ESA therapy have been reported to induce hypertension.[31] Furthermore, the hypertensive effects of ESA could be augmented in uremic and hypertension-predisposed animals.[32] ESA also affects contraction of the vascular endothelium. Noguchi, et al.[33] reported that endothelial NO synthesis was suppressed and vasodilating responses were decreased in rabbits treated with ESA for one week.

Investigating the risk of vascular access failure is valuable as it is the cause of inconvenience, discomfort, and morbidity.[5] Vascular access failure has been reported as the leading cause for hospitalization and morbidity in patients with ESRD.[3,34,35] Furthermore, it is associated with high costs.[23] The ESRD prevalence is increasing,[36] and the costs of caring of this population have also increased. The reported cost of access failure in the United States in 1996 was approximately one billion dollars.[37] The United States Renal Data System reported HD access failure as the most frequent cause of hospitalization for CKD patients.[38]

Furthermore, increased use of ESA for the treatment of anemia in CKD patients and the possibility of it being an important risk factor for AVF failure are reasons it is important to elucidate the relationship between ESA and AVF failure, including dose-effect outcomes. Our study differs from previous clinical studies in that we selected patients who had matured AVF access and calculated mean ESA doses and hemoglobin levels during the whole study period. Based on our results it is reasonable to assume that ESA dose may be a significant risk factor, irrespective of hemoglobin level, because the mean hemoglobin levels were comparable between the two groups.

This study has several limitations. It was a small, cross-sectional study. We only included laboratory data collected at the time of AVF formation. Because we depended on data from medical records only, the other possible effects of smoking history and intra-access blood flow could not be included. Even though all patients had initiated AVF cannulation successfully within 3 months since AVF formation, we could not evaluate AVF maturation by objective methods, such as access flow, depth from skin surface, or fistula diameter. Furthermore, we only proposed that ESA might indirectly promote neo-intimal hyperplasia, and no pathophysiological mechanisms were explored in our study. Because we did not perform imaging or intervention on all AVFs in the control group, we could not elucidate whether focal hyperplasia might be present in control patients during the study period.

In conclusion, we have demonstrated an association between ESA dose and late AVF failure, which suggests that ESA may contribute to late AVF failure, although causality was not shown. Further evaluation of ESA effects on late AVF patency failure with a larger patient population and longer follow-up period, as well as a direct investigation on whether ESA promotes neo-intimal hyperplasia in late AVF failure, are necessary to confirm our results.

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