

## Should Endovascular Intervention be the First Choice to Treat Central Vein Stenosis in Hemodialysis Population?

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### Abstract

**Purpose:** To evaluate the clinical features and the survival benefits of Chinese hemodialysis (HD) patients with central vein stenosis (CVS) undergoing different treatments.

**Methods:** From January 1, 2011 to Dec 31, 2012, 116 HD patients at high risk of CVS at our hospital had their bilateral central veins assessed by vascular ultrasound and conventional venography. We compared the clinical outcome of 24 non-treated asymptomatic, 17 non-treated symptomatic CVS and 6 treated symptomatic CVS. Treatment costs of CVS were recorded and patients' survival rates were estimated by Kaplan-Meier analysis.

**Results:** Among 116 patients, 47 were diagnosed with CVS. The timespan between symptomatic presentation and the diagnosis of CVS was more than 10 months averagely. Compared with non-CVS patients, the duration of HD in CVS patients was longer ( $33.8 \pm 14.5$  vs  $1.1 \pm 0.7$  months) and the rate of central venous catheter (CVC) insertion was higher (87.2% vs 14.5%). Only 6 patients tried to maintain vascular access by endovascular intervention, the cost for which was \$5210 per person, much higher than other treatment options. While 30 patients refused endovascular intervention for fear of re-stenosis risk and high treatment costs, among whom 28 lost their initial vascular access. The 12-month survival rates were 87.8%, 60% and 80.3%, respectively. The 24-month survival rates were 48.8%, 60% and 42.8%, respectively. No significant difference was found among the three groups.

**Conclusions:** Endovascular intervention may not be the first choice for HD patients with CVS, considering long term survival benefit and high treatment cost.

**Keywords:** Central vein stenosis; Hemodialysis; Venography; Endovascular intervention; Survival analysis

### Introduction

Central venous catheter (CVC) is often required as temporary or long-term vascular access for many HD patients in China. It has been associated with an increased risk of CVS [1-3]. As HD patients live longer, we are facing a growing number of patients with CVS. Endovascular intervention, such as percutaneous transluminal angioplasty (PTA) with or without stenting is now recommended as the initial intervention for HD patients with CVS [4-6]. But their recommendations did not cover economic factors and survival benefits. And in China, few CVS are diagnosed in HD patients until symptoms such as facial swelling or unilateral upper limb edema appeared. Endovascular intervention for HD access can only be performed in a few big hospitals in big cities. The current situation of CVS in HD patients in China needs to be evaluated. Survival benefits and economic factors of patients should also be considered to balance the advantage and the disadvantage of endovascular intervention. Our purpose is to evaluate the clinical features and the survival benefits of Chinese HD patients with CVS undergoing different treatments.

### Materials and Methods

CVS was defined as stenosis or occlusion of the internal jugular vein, subclavian vein, brachiocephalic vein, superior vena cava, femoral vein, iliac vein or inferior vena cava. Thrombus, angulation, compression and/or peri-catheter sleeve formation are also detected in our study.

We performed a prospective study. From January 1, 2011 to Dec 31, 2012, 116 HD patients at high risk of CVS at our hospital had their bilateral central veins tested by vascular ultrasound and conventional venography. Informed consent was obtained from each patient. Patients under 18 or refusing venogram were excluded.

Patients at high risk of CVS enrolled in conventional venogram included:

(1) Patients preparing for arteriovenous fistula (AVF) creation with ipsilateral CVC (temporary or permanent hemodialysis catheters-PHC) or with history of ipsilateral CVC and/or central venous operations (including peripherally inserted central catheters-PICC, pacemaker and defibrillator wires); (27 patients)

(2) Patients awaiting insertion of permanent hemodialysis catheter (PHC); (60 patients)

(3) Patients with dysfunctional CVC (temporary catheter or PHC) which failed to be restored by thrombolysis for 3 consecutive days or whose CVC dysfunction happened for 3 times in 6 months; (16 patients) and

(4) Patients with facial or breast swelling and/or unilateral upper limb edema, collateral formation, and thus were suspected to have CVS (13 patients).

Information was recorded about patient demographics, medical histories, symptoms at presentation, the duration of HD, the duration

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of CVC, the time between symptomatic presentation and the diagnosis of CVS, the time between commencement of HD and surgical access creation, the number and side of vascular access operations prior to the diagnosis of CVS, treatment choices and treatment costs. Before venogram, all patients' bilateral internal jugular vein, subclavian vein, femoral vein and iliac vein were detected with vascular ultrasound.

Bilateral peripheral venipuncture and/or bilateral internal jugular vein puncture were performed in patients with angiocath (20G, BD Medical Apparatus Corporation, Ltd) at the time of venogram. Peripheral venipuncture was also done via existing AVF. Ipsilateral internal jugular vein puncture was stopped in patients with stenosis, thrombosis or occlusion in internal jugular vein, detected by vascular ultrasound. If patients had a CVC that was ready to be removed at the time of study, venogram would be performed through the catheter [7]. Three patients had femoral vein and iliac vein venogram performed through femoral vein catheter. At the end of the examination, safety venous in dwelling needles or the catheters were pulled out completely from the patient and manual pressure was applied at the insertion site for 5min. Each patient was injected with total 40 ml to 60 ml non-ionic contrast material.

All the images were assessed by ultrasonic doctor, interventional radiologist and nephrologist familiar with every kind of CVS. Bilateral internal jugular vein, subclavian vein, brachiocephalic vein and superior vena cava were assessed in all patients; in addition bilateral femoral vein and iliac vein were assessed in patients with femoral vein catheter. For each case were recorded the presence of pericatheter sleeve around the catheter, thrombus formation (or any filling defect in the vein or on its wall), the diameter and stenosis of the central veins. CVS less than 49% was defined as mild, CVS of 50% to 69% was defined as moderate and CVS of 70% or greater was defined as severe. Symptomatic CVS or CVS potentially interfering vascular access for HD were selected to be treated.

All patients were instructed to inform their nephrologists if they developed any complaints related to contrast injection after the venographic study.

Treatment options include: (1) endovascular intervention (including PTA/stent); (2) avoiding ipsilateral CVS to create arteriovenous fistulas (AVF) and arteriovenous grafts (AVG), PHC; (3) switching to PD; (4) thrombolysis; (5) maintaining the original vascular access surgery without any treatment. And then, patient follow-up was carried out every 1-3 months by a nephrologist.

The endpoint of the follow-up:

Patients die or give up dialysis.

Patients switch to kidney transplantation.

Expiry of deadline: Aug 1, 2013.

Chi-square and Fisher's exact tests were used as appropriate to analyze categorical variables, and the student's t-test was used to analyze continuous variables. Patient's survival rates were determined with Kaplan-Meier curves. Probability values <0.05 were accepted as significant.

## Results

Clinical characteristics of patients with and without CVS were shown in Table 1 116 out of 245 hemodialysis patients at our hospital were enrolled in the study. 6 patients without ipsilateral history of CVC or central venous operation were diagnosed with CVS; No CVS was

found in 2 patients who presented arm edema ipsilateral to functioning AVF. In our study, younger patients are more likely to choose AVF as the initial vascular access, while patients older than 70 preferred PHC. This inclination affect the HD duration of patients in Table 1.

Clinical presentations of CVS in our patients were shown in Table 2. 11 patients presented facial swelling and/or unilateral upper limb edema; 8 of the 11 had ipsilateral functioning AVF (3 of the 8 patients had history of several ipsilateral AVF creations but no history of ipsilateral CVC or central venous operation); 3 of the 11 were patients with PHC. The timespan between symptomatic presentation and the diagnosis of CVS was 14.0±6.8 months. 6 of the 11 patients had their ipsilateral functioning AVF closed and contralateral AVF created. 3 patients received PTA and/or stent. 2 of the 3 got technical success; another patient turned to contralateral AVF creation after PTA failed. One patient chose the thrombolytic treatment. Several days later, his symptom (unilateral upper limb edema) was partially relieved. One 86 years old patient refused all treatment. Twelve patients presented CVC dysfunction. The timespan between CVC dysfunction and the diagnosis of CVS was 10.4 ± 4.9 months. For 3 of the 12, dysfunctional CVC were pulled out and a new PHC were inserted in another central vein (2 left internal jugular vein, 1 right femoral vein); 4 of the 12 switched to PD; 2 of the 12 had successful contralateral AVF creations; 2 of the 12 were replaced with a 45 cm PHC to inferior caval vein in situ after a successful PTA. The last patient was detected thrombus in right internal jugular vein, thus an optional filter was placed into his superior vena cava, then a 36cm PHC was inserted in situ after the temporary dysfunctional CVC was pulled out. 24 patients (51.1%) were asymptomatic; 4 of them who had a planned AVF site were changed to contralateral arms; 9 of them who had a planned PHC site were changed to contralateral central veins, and another 11 patients

	CVS	Non-CVS
No. of patients	47	69
Presentations of CVS	58	
Duration of HD (Months)	33.8 ± 14.5'	1.1 ± 0.7
Vascular ultrasound diagnosis	15	0
Venogram diagnosis	39	0
Mean ages (years)	62.3 ± 11.2'	70.2 ± 10.1
Male	23 (48.9%)	36 (52.2%)
History of CVC	41 (87.2%)	10 (14.5%)
Cause of ESRD		
Glomerulonephritis	10 (21.3%)#	7 (10.1%)
Diabetes mellitus	14 (29.8%)#	31 (44.9%)
Hypertension	17 (36.2%)	25 (36.2%)
Others	6 (12.8%)	6 (8.7%)

\*p<0.001, compared with non-CVS group, #p<0.05 compared with non-CVS group.

CVS: Central Venous Stenosis; HD: hemodialysis; CVC: Central Vein Catheters; ESRD: End Stage Renal Diseases

**Table 1:** Clinical characteristics of CVS patients and non-CVS patients.

	Number of patients	Time between symptomatic presentation and the diagnosis of CVS (months)
Facial swelling and / or unilateral upper limb edema	11 (23.4%)	14.0 ± 6.8
CVC dysfunction	12 (25.5%)	10.4 ± 4.9
Asymptomatic	24 (51.1%)	

CVS: Central Venous Stenosis; CVC: Central Venous Aatheter

**Table 2:** Clinical symptoms of CVS in 47 patients.

were preserved with the planned vascular access surgery. All treatment options were summarized in Table 3.

Different treatment options and treatment costs (including DSA facility costs, professional fees and devices fees, such as balloon, stent or guidewire) related to CVS were shown in Table 3. Only 6 patients tried to maintain vascular access by endovascular intervention, the cost for which was \$5210 per person; 28 patients refused endovascular intervention and lost their initial vascular access, and 2 patients refused surgical treatment and endovascular intervention still presented arm edema ipsilateral to functioning AVF; 11 asymptomatic CVS patients did not need specific treatment for their HD vascular access.

47 patients diagnosed with CVS were divided into 3 groups: non-treated symptomatic CVS (group A, n=17), treated symptomatic CVS (group B, n=6) and non-treated asymptomatic CVS (group C, n=24). The average ages in the three groups were  $59.7 \pm 15.0$ ,  $64.8 \pm 14.5$  and  $63.0 \pm 14.9$ , with no significant difference ( $p > 0.05$ ). 6-month survival rates among the three groups were 94.1%, 80% and 91.3%. 12-month survival rates were 87.8%, 60% and 80.3%. 18-month survival rates were 73.3%, 60% and 71.3%. And 24-month survival rates were 48.8%, 60% and 42.8%. Survival rates were not significantly different among the three groups ( $p > 0.1$ ) (Figure 1).

## Discussion

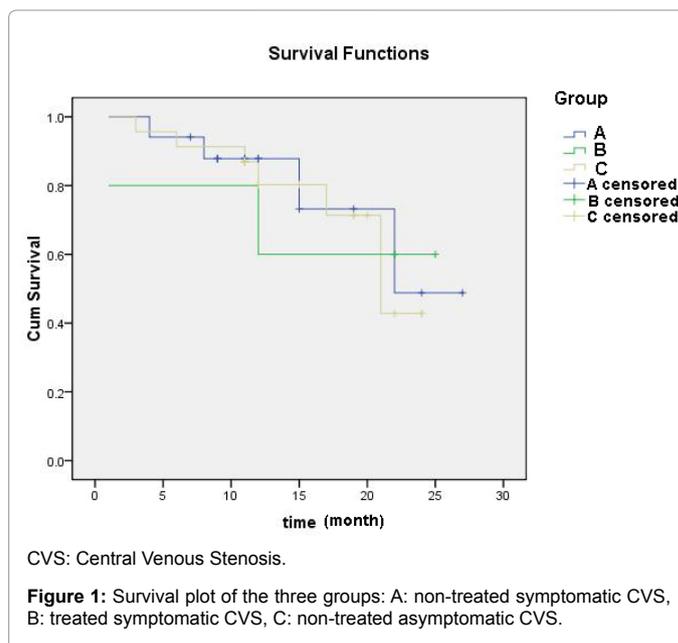
Indications for venogram were set according to medical conditions in Wuhan, published literatures and clinical practices. CVC has been associated with an increased risk of CVS in HD patients [1-3]. Oguzkurt et al. [7] showed that even short-term catheters would result in significantly high rates of pericatheter sleeve, thrombus formation and CVS. In our study, the rate of CVC insertion in the CVS patients was significantly higher (87.2%) than that of in the non-CVS patients (14.5%), which was similar with previous studies [8,9]. Several references [10,11] also suggested that the use of venogram may help to minimize the risk of complications from the CVC insertion procedure, and catheters may be inserted with fluoroscopic guidance. If CVC dysfunction occurred repeatedly, pericatheter sleeve and CVS should be considered and detected by venogram. CVS should be suspected in patients with facial swelling and/or unilateral upper limb edema, collateral formation, and then it should be detected by venogram [4,12].

Our study suggests the necessity for bilateral central vein ultrasound and venogram for every patient at high risk of CVS. Several published studies did not describe whether the venogram was made through bilateral or unilateral central vein, while others showed that

	Treatment options	Treatment costs
Change AVF site to contralateral arm	12	\$277
Change PHC site to other central vein	12	\$1140
Switch to PD	4	\$410 to \$980 (in average of \$690/person)
Endovascular therapy	6	\$1630 to \$10590 (in average of \$5210/person)
Thrombolysis	1	\$50
Refused any treatment	1	\$0
Maintain the original vascular access surgery without any treatment	11	\$277

AVF: Arteriovenous Fistulas; PHC: Permanent Hemodialysis Catheters; PD: Peritoneal Dialysis

**Table 3:** Different treatment options and treatment costs of CVS.



the venogram was made through unilateral catheter [3,6,7,11]. In our study, bilateral central veins were assessed. 58 CVS were diagnosed in 47 patients. 24 patients were asymptomatic and 6 patients with CVS had no history of ipsilateral CVC or central venous operation. Some CVS will be neglected if central vein assessment is not performed bilaterally. Vascular ultrasound is noninvasive, cheap and generally accepted by patients. So, bilateral vascular ultrasound and venography were combined in our study to assess vascular access.

No appropriate guideline was generally accepted due to lack of definitive studies of asymptomatic CVS with endovascular intervention. So empiric treatment of asymptomatic CVS is commonly practiced. Recently, Renaud et al. [13] suggested that withholding treatment in asymptomatic/pauci-symptomatic CVS in dialysis fistulas yielded significantly better short- and long-term central vein patency than treatment of symptomatic cases without detrimental effects on overall dialysis circuit. Levit et al. [14] also suggested that PTA of asymptomatic CVS greater than 50% in the setting of hemodialysis access maintenance procedures was associated with more rapid stenosis progression and escalation of lesions, compared with a non-treatment approach. These studies suggested that non-treatment option was better than treatment in asymptomatic CVS. So, in our study, 24 asymptomatic CVS patients were not treated with endovascular intervention.

Most literatures [4-6], including the K/DOQI guidelines [15], recommend PTA, with or without stent placement as the preferred treatment approach to symptomatic CVS. Treatment with PTA and/or stents is beneficial in maintaining dialysis access circuit patency (including AVF, AVG and PHC) [5,13,14,16-18] and alleviating swelling of the ipsilateral arm, breast, or face in the short term [19]. But re-stenosis is one of main risks for treated CVS [20,21]. For PTA, there is a 6-month primary patency range of 23% to 63% and a 12-month primary patency range of 12% to 50%. For Bare metal stents (BMSs), there is a 6-month primary patency range of 42% to 89% and a 12-month primary patency range of 14% to 73% [19,22-25]. For covered stents (CSs), further randomized controlled trials, with long-term follow-up will be necessary [6]. It is apparent that repeated interventions are required with PTA/stent for CVS, to maintain patency over the long

term. Repeated interventions will not be easily accepted by patients for fear of treatment risks and heavy financial burden.

Heavy financial burden is one of the main reasons for most of our patients to refuse endovascular intervention. The medical insurance payment system is one of the important factors to influence treatment options. In China, medical expense for endovascular intervention will be partially covered by medical insurance only when patients are hospitalized, but the rest is still too expensive. 6 symptomatic CVS patients were treated with endovascular intervention, the cost for which was \$5210 per person for a single course of treatment. While others spent less than \$1140 per person. Most patients preferred less expensive treatments to resolve their problems in vascular access even though they lost their initial access and turned to contralateral access or to PD.

We are interested in whether different treatment approaches will affect patients' survival. So, patients' survival rates were compared among non-treated symptomatic CVS, treated symptomatic CVS and non-treated asymptomatic CVS. No significant difference was found among the three groups in our study. Patients in non-treated groups all got access to continue dialysis. For access patency, no generally accepted evidence has shown that endovascular intervention had more benefit in maintaining hemodialysis access patency over the long-term than other treatment options. Considering the advantage and the disadvantage, we think that endovascular intervention is one of the alternative treatment options for CVS, but not the first-line choice. The indications of endovascular intervention should be strictly limited to symptomatic CVS. More treatment options should be provided, tailored to the individual patient.

Attention should be given to the fact that patients lost treatment opportunity in early stage of CVS due to the long timespan (more than 10 months) between symptomatic presentation and the diagnosis of CVS.

Further randomized control studies are needed to evaluate the risk and the benefit of endovascular intervention in more patients, with long-term follow-up.

## Conclusions

Endovascular intervention is one of the alternative treatment options for CVS, but not the first-line choice. CVC increased risk of CVS in HD patients, thus avoiding CVC is the best way to prevent CVS.

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