Central Venous Stenosis, Access Outcome and Survival in Patients undergoing Maintenance Hemodialysis

Anamika Adwaney, Charlotte Lim, Sarah Blakey, Neill Duncan, and Damien R. Ashby

Abstract

Background and objectives Central venous catheters have traditionally provided access for urgent hemodialysis, but are also sometimes advocated as an option for older or more comorbid patients. Adverse effects of this type of dialysis access include central venous stenosis, for which the risk factors and consequences are incompletely understood.

Design, setting, participants, & measurements We conducted two studies within the same population cohort, comprising all patients starting hemodialysis in a single center from January 2006 to December 2013. First, patients were retrospectively analyzed for the presence of central venous stenosis; their access outcomes are described and survival compared with matched controls drawn from the same population. Second, a subset of patients with a history of catheter access within this cohort was analyzed to determine risk factors for central venous stenosis.

Results Among 2811 patients, central venous stenosis was diagnosed in 120 (4.3%), at a median dialysis vintage of 2.9 (interquartile range, 1.8–4.6) years. Compared with matched controls, patients with central venous stenosis had similar survival (median 5.1 versus 5.2 years; P=0.54). Among a subset of 500 patients, all with a history of catheter use, 34 (6.8%) developed central venous stenosis, at a rate of 2.2 per 100 patient-years. The incidence of central venous stenosis was higher with larger number of previous catheters (relative risk [RR], 2.2; 95% confidence interval [95% CI], 1.6 to 2.9), pacemaker insertion (RR, 3.9; 95% CI, 1.7 to 8.9), and was lower with older age (RR, 0.7 per decade; 95% CI, 0.6 to 0.8). In a Cox proportional hazards model, the catheter number, pacemaker, and younger age at dialysis initiation were all significant independent risk factors for central venous stenosis.

Conclusions Central venous stenosis occurred in a minority of patients on hemodialysis, and was associated with compromised future access, but unchanged survival. Among patients with a history of catheter use, risk related to both the number of catheters and the total catheter duration, although nondialysis factors such as pacemakers were also important. Central venous stenosis was lower in older patients, supporting the selective use of tunneled catheters in this group.


Introduction

The arteriovenous fistula is widely regarded as the best long-term hemodialysis access, whereas tunneled catheters have traditionally provided access for urgent dialysis, or when a fistula has not been successful (1,2). Fistula outcomes, however, are suboptimal, with primary failure and delayed maturation occurring in about a third of cases, so that multiple procedures are often required, which can lead to patient fatigue and fistula refusal (3–5).

The demographic changes in the dialysis population over the past decade have also adjusted the access landscape, with older and more comorbid patients making up a greater proportion (6,7). These patients have both poorer fistula outcomes and shorter life expectancy, and although fistula formation is still desirable it may be less tolerable (8–10). Catheters are increasingly advocated as a long-term access option for some elderly and more comorbid patients. This approach is supported further by the observation that the principal catheter complication, bacteremia, may occur less frequently in this group (11).

Another concern over catheter use is central venous stenosis. Less studied than infection, the pathogenesis is poorly understood, but it is thought to involve elements of trauma, inflammation, and coagulation, and many important clinical questions remain unanswered (3,12–14). Although central venous stenosis is known to be associated with catheter access, it does not affect all patients after a catheter, and it is unclear whether the extent of catheter use or other factors account for this variability. In addition, although commonly associated with access dysfunction, there are limited data on subsequent access and other clinical consequences are highly variable, ranging from asymptomatic to severe, and so the effect of central venous stenosis on patient survival is unknown (9–11). The aim of this study is therefore to investigate the risk and clinical consequences of central venous stenosis in a large hemodialysis cohort by describing long-term clinical
outcomes in those affected, and analyzing risk in a cohort of patients with catheter exposure.

Materials and Methods

Study Population

All patients who started hemodialysis at a single kidney center from January 2006 to December 2013, because of failure of their own kidneys, a change in kidney replacement modality, or a transfer from another center, were identified. The center consists of a dialysis unit at the main institution and eight satellite units across West London, UK.

Selection of Cases and Matched Controls

In the main cohort study, patients with a diagnosis of central venous stenosis were identified from electronic records of conventional angiography and time-resolved magnetic resonance venograms, along with the context in which the imaging was planned. Case finding was carried out in 2017, around 3–11 years after dialysis initiation. Central venous regions were divided into superior vena cava or brachiocephalic/subclavian vein, and stenosis was defined by extent (>50% reduction) or the requirement for balloon venoplasty, with cases confirmed by at least two investigators.

Survival in those with central venous stenosis was compared with that of a matched control group within the cohort. Matching was performed manually according to an algorithm that selected a noncase for every case, identical in sex and comorbidity (diabetes and prior vascular events), with hemodialysis vintage at least as long, matched as closely as possible for age (always within 5 years). One patient with central venous stenosis could not be matched with this algorithm and was excluded. The matched control group was used to assess patient survival only.

In the second study, a subset of 500 patients unaffected at baseline, receiving hemodialysis for at least 6 weeks, was selected at random from the same population to allow detailed extraction of risk factor data. Because the association of catheters is epidemiologically well established, only patients with a history of catheter use were included; the nature and extent of catheter exposure was recorded, including catheter type, location, number of catheters, and overall catheter duration. Central venous stenosis in this subset was identified through examination of all imaging, ensuring all identifiable cases were captured, to minimize bias. Potential risk factors were assessed from electronic records.

Study Outcomes

Access procedures, including venoplasty and new access formation, were assessed in patients with central venous stenosis from the time of diagnosis. Access failure was defined as permanent abandonment and requirement for new access, with procedural or urokinase assistance not treated as failure. Survival for patients on hemodialysis was compared in patients with central venous stenosis and the matched control group. Risk factors for the development of central venous stenosis were assessed in the subset of 500 patients, unaffected at baseline, who remained on hemodialysis for at least 6 weeks, with a history of catheter access. Complete survival and access data were available for all patients unless they transferred to another center. Most clinical data were available, but intensive care unit admissions could only be ascertained when occurring at the main institution (unknown comorbidities were coded as absent).

Statistical Analyses

In the main cohort study, access survival among the entire cohort was analyzed by Kaplan–Meier method, with access failure as the event, censoring for access redundancy, modality change, death, and moving to another center. The Kaplan–Meier method was also used to analyze patient survival both with and without censoring for transplantation, censoring for moving out of area. In the 500-patient sub-study, the association between potential risk factors and the incidence of central venous stenosis was analyzed singly using rate ratios and chi-squared tests. Catheter duration and number were treated as time-varying exposures in a univariable analysis. Multivariable analysis of risk factors was performed using a Cox proportional hazards model to assess hemodialysis duration without central venous stenosis, censoring for death, modality change, and transfer out of area. Catheter duration and number were fixed covariates in this model, with duration expressed as a proportion of total time, using the final catheter number before the diagnosis of central venous stenosis or the end of observation. SPSS v22.0 (IBM, New York, NY) was used for statistical modeling.

Results

Characteristics

During the study period 2811 patients (aged 16–91 years, mean 61 years, 63% male) started hemodialysis. By the end of a mean observation period of 4.5 years, most patients were no longer on hemodialysis (44% of patients had died and 30% had changed modality or recovered) and the 26% who remained on hemodialysis had been observed for a mean of 4.7 years. Central venous stenosis had been identified radiologically in 120 patients (4.3%).

The diagnosis of central venous stenosis was made at a median dialysis vintage of 2.9 (interquartile range, 1.8–4.6) years, and was preexistent in four patients at the outset of the study: two patients transferred from another dialysis center with known central venous stenosis, and two had central venous stenosis at dialysis initiation (one after a decade of parenteral nutrition and one unexplained). Clinical characteristics of affected patients are shown in Table 1. Typical focal symptoms (headaches or facial/arm swelling) were reported in 16%, whereas potentially related, generalized symptoms (low BP or inability to achieve target weight) were present in 8%. These symptoms contributed to the diagnosis in some patients, but the majority (76%) was asymptomatic, with the diagnosis made when planning or performing access procedures.

Figure 1 shows the regions involved among all patients with central venous stenosis. Disease was bilateral, affecting either the superior vena cava or both brachiocephalic veins, in 64 patients (53%), and a greater proportion of these patients had symptoms compared with those with unilateral disease (30% versus 16%; P=0.11). In five patients, the venous pathology was remote from any previous catheter site, but catheter use could have accounted for 96% of cases.
Patient Survival

After a mean observation period of 3.5 years, 16% of patients with central venous stenosis had a functioning transplant, 47% had died, 2% had moved out of area, and 35% remained on dialysis in this center. Although no patient died of absent access, in four patients, central venous stenosis may have been a contributory cause of death at 2.1–7.8 years postdiagnosis.

Mortality in those with central venous stenosis was compared with a group of unaffected patients drawn from the same cohort (Table 1), and matched for age at hemodialysis initiation, sex, diabetes/vascular comorbidity, and hemodialysis vintage (at the time of diagnosis), with survival censored for moving out of area. One patient (who remained alive at the end of observation) could not be matched and was excluded from this analysis. Compared with unaffected matched patients, survival in patients with central venous stenosis was similar (median 5.1 versus 5.2 years; $P=0.54$; mean observation 3.5 and 3.6 years, respectively; Figure 2). The same lack of mortality difference was observed when censoring for transplantation, and when restricting the analysis to patients with central venous stenosis with bilateral disease ($n=63$) and their matched controls.

Access Outcome

After the diagnosis of central venous stenosis, during a mean dialysis observation period of 2.9 years, 240 further hemodialysis access procedures were performed in 110 patients, including catheter insertion (with or without venoplasty) and fistula or graft formation. The mean number of access procedures was two per patient (range 0–16), with a right-skewed distribution so that eight patients had more than five further access procedures. Most of these were in the superior vena cava territory, including catheter insertion through stenosis ($n=176$), catheter insertion not through stenosis ($n=17$), and arteriovenous fistulas or graft formation ($n=6$), but there were 13 patients who required a total of 41 access procedures in the inferior vena cava territory, including inferior vena cava catheters ($n=31$), femoral vein catheters ($n=9$), and femoral grafts ($n=1$).
Median patency (procedure-assisted, censored for redundancy) for fistulas and grafts was 27 months, whereas for catheters in the superior vena cava territory, inferior vena cava, and femoral vein, median patency (urokinase-assisted, censored for redundancy) was 20, 8, and 2 months, respectively. Of the two most common locations, catheters in the superior vena cava territory were significantly more durable than those in the inferior vena cava ($P=0.01$). In the control group, from the vintage-matched time point, median patency for fistulas was 58 months, and for catheters (all superior vena cava territory) it was 38 months.

**Risk Factors**

Risk factors were determined in a subset of patients, randomly selected from those with a history of catheter use, undergoing hemodialysis for at least 6 weeks, and without preexistent central venous stenosis (Supplemental Table 1). Patients were observed until the end of their hemodialysis career in 72% (mean duration 2.6 years), whereas those remaining on hemodialysis were observed for a mean of 5.2 years (mean duration 3.0 years overall). Among 500 patients (aged 17-90 years, mean age 62 years, 65% male) central venous stenosis developed in 34 (6.8%) patients, at a rate of 2.2 per 100 patient-years.

The risk of central venous stenosis was closely related to the amount of catheter exposure, with incidence increasing progressively across categories of catheter duration (relative risk [RR], 1.4 per catheter-year; 95% confidence interval [95% CI], 1.1 to 1.6) and number of catheters (RR, 2.2 per additional catheter; 95% CI, 1.6 to 2.9; Figure 3). In addition, incidence of central venous stenosis was greater after a left-sided catheter (RR, 2.6; 95% CI, 1.2 to 4.4), and with a history of single (dual lumen) as opposed to twin (tesio) catheters, the latter being the predominant catheter type.

Nondialysis risk factors increasing the incidence of central venous stenosis included transvenous pacemakers (RR, 3.9; 95% CI, 1.7 to 8.9), and previous intensive care unit admission. In particular, age at dialysis initiation was also a strong risk factor, with the incidence of central venous stenosis decreasing progressively across increasing age categories (RR, 0.7 per decade; 95% CI, 0.6 to 0.8; Figure 4). To adjust for the competing effect of mortality on the incidence of central venous stenosis in older patients, a Cox proportional hazards model was fitted, censoring for death, modality change, or moving out of area; in this model catheter number, pacemaker and age at dialysis initiation were all independently associated with the time to develop central venous stenosis (Table 2).

No significant associations were found between central venous stenosis and sex, ethnicity, comorbidity, or type of primary kidney disease.

**Discussion**

In this cohort of patients undergoing hemodialysis followed for their entire hemodialysis career or an average of 4.7 years, 4.3% were affected by central venous stenosis. In those with a history of catheter use, central venous stenosis developed with an incidence of 2.2 per 100 patient-years. These rates are comparable with other studies of clinically noticeable central venous stenosis, such as Wang et al., who reported 9% of patients affected (4). However, as expected, they are lower than studies using population screening, such as Guo et al.’s (15) computed tomography–based study (35%) and studies performed in enriched populations, such as MacRae et al.’s study of patients with access difficulty (41%) (9,16).

In this study, future access function was compromised in patients with central venous stenosis, with further
intervention required in the majority, and with a minority suffering significant therapeutic burden with more than five further procedures (1). The majority of patients had continued catheter use after the diagnosis of central venous stenosis; individual data on these decisions are not available but both access site exhaustion and patient preference may have been influential. Where it could be achieved, superior vena cava territory access was superior to inferior vena cava territory, being roughly twice as durable, highlighting the advantage of maintaining patients on superior vena cava territory access where possible.

Three quarters of affected patients in this study were asymptomatic, with the diagnosis made at the time of access intervention, emphasizing the need for a high index of suspicion with this diagnosis. Bilateral disease was more commonly symptomatic, and a minority of these patients had severe clinical features, with the condition being a contributory cause of death in a few patients. This raises the possibility that central venous stenosis may shorten survival without being recognized as contributing; the observation that affected patients had comparable survival to matched controls argues against this, but this does not

Figure 3. Catheter duration and the total number of catheters were risk factors for central venous stenosis. Incidence of central venous stenosis among 500 patients on haemodialysis with a history of catheter access, by catheter duration and number of catheters (P value for linear trend, patient-years for each category shown as gray bars, total patient-years=1571).

Three quarters of affected patients in this study were asymptomatic, with the diagnosis made at the time of access intervention, emphasizing the need for a high index of suspicion with this diagnosis. Bilateral disease was more commonly symptomatic, and a minority of these patients had severe clinical features, with the condition being a contributory cause of death in a few patients. This raises the possibility that central venous stenosis may shorten survival without being recognized as contributing; the observation that affected patients had comparable survival to matched controls argues against this, but this does not

Figure 4. Risk of central venous stenosis was lower in older patients. Incidence of central venous stenosis among 500 patients on haemodialysis with a history of catheter access, by age at dialysis initiation (P value for linear trend, patient-years for each category shown as gray bars, total patient-years=1571).
The most surprising finding of this study was the strong relationship between age at dialysis initiation and central venous stenosis risk, with every decade reducing risk by about a third. It is important to note that this was robust in adjusted models, and therefore was not due to confounding by catheter number or dialysis duration, but rather to age alone. A hint of this relationship has been observed previously, with Napalkov et al. finding more catheter complications in adolescents than adults, but the finding that older adults experience a lower risk of central venous stenosis has not been reported before (21). This is of clinical relevance, underlining the importance of catheter avoidance in young adults as well as being consistent with a diminished fistula advantage in older age groups (20,22). Because older patients also have poorer fistula outcomes, some authors have questioned the wisdom of a universal “fistula-first” strategy in this group, concluding that clinical equipoise may exist between access strategies in the elderly (23,24). The finding that elderly patients have a lower risk of central venous stenosis is supportive of studies exploring elderly-specific approaches to dialysis access.

Although complete prospective records were available for dialysis initiation and radiology, the data in this study was retrospectively extracted and analyzed, and this study was restricted to a single center, which may also limit the generalizability of conclusions. However, the patient cohort is both large and internally consistent in terms of diagnostic and management strategies.

Importantly in this study, cases were found through preexisting radiology, and patients were not systematically screened for the presence of central venous stenosis, so it is acknowledged that a number subclinical cases would not have been identified. The group of cases studied would therefore be incomplete and possibly unrepresentative. However, the lengthy follow-up period was sufficient to cover the complete dialysis career of most patients, so it seems likely that most of the missed subclinical cases would not have resulted in symptoms, therefore although the incidence may be underestimated, the clinical effect of central venous stenosis is more likely to be overestimated. In the analysis of dialysis-related risk, significant

### Table 2. Risk factors for central venous stenosis among 500 patients on hemodialysis using a catheter for dialysis access

<table>
<thead>
<tr>
<th>Variables Included</th>
<th>Per Unit</th>
<th>Unadjusted HR (95% CI)</th>
<th>P value</th>
<th>Adjusted HR (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at dialysis initiation</td>
<td>10 yr</td>
<td>0.60 (0.43 to 0.74)</td>
<td>&lt;0.001</td>
<td>0.60 (0.48 to 0.74)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Pacemaker</td>
<td>Yes versus no</td>
<td>3.87 (1.67 to 8.95)</td>
<td>0.002</td>
<td>4.25 (1.81 to 9.99)</td>
<td>0.001</td>
</tr>
<tr>
<td>No. of catheters</td>
<td>Catheter</td>
<td>2.15 (1.37 to 3.37)</td>
<td>0.001</td>
<td>1.97 (1.24 to 3.13)</td>
<td>0.004</td>
</tr>
<tr>
<td>Variables excluded</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Previous ICU admission</td>
<td>Yes versus no</td>
<td>2.02 (0.96 to 4.26)</td>
<td>0.06</td>
<td>0.20</td>
<td></td>
</tr>
<tr>
<td>Catheter duration</td>
<td>1 yr</td>
<td>1.05 (0.99 to 1.11)</td>
<td>0.07</td>
<td>0.31</td>
<td></td>
</tr>
<tr>
<td>Single (dual lumen) catheter</td>
<td>Yes versus no</td>
<td>4.03 (1.39 to 11.7)</td>
<td>0.01</td>
<td>0.50</td>
<td></td>
</tr>
<tr>
<td>Left-sided catheter</td>
<td>Yes versus no</td>
<td>1.60 (0.80 to 3.19)</td>
<td>0.18</td>
<td>0.81</td>
<td></td>
</tr>
</tbody>
</table>

Cox proportional hazards model for hemodialysis survival without central venous stenosis among 500 patients on hemodialysis with a history of catheter dialysis access. Final model adjusted for age at dialysis initiation, pacemaker, and number of catheters, censoring for death, modality change, and transfer out of area. Number of events with pacemaker=7, with ICU admission=10, left-sided catheter=16, with single catheter=4, and total=34. HR, hazard ratio; 95% CI, 95% confidence interval; ICU, intensive care unit.
collinearity between factors (in particular, number of catheters and left-sided location) may have biased the relative strengths of the associations and argues for a degree of caution in their interpretation.

In summary, in patients undergoing hemodialysis with a history of catheter access, a significant minority may develop central venous stenosis, although most patients are asymptomatic, and the diagnosis does not statistically affect survival. Risk relates both to the number of previous catheters and their combined duration. Considerable risk may be conferred by factors unrelated to dialysis, such as pacemakers. The observation that patients aged >70 years, and especially those >80 years, are less likely to develop central venous stenosis, supports the selective use of tunneled catheters as permanent access in elderly patients undergoing dialysis.

Acknowledgments
D.R.A. and A.A. were involved in the design of the study. A.A., C.L. and S.B. collected and summarized the data. Statistical analysis was performed by D.R.A. The initial draft of the manuscript was written by A.A., subsequently revised by D.R.A. and N.D., and then agreed by all authors.

Disclosures
D.R.A. has received a speaker’s honorarium from Fibrogen. This project was partially funded by a Research Fellowship awarded by Imperial Health Charity (grant reference RF17/1041).

Supplemental Material
This article contains the following supplemental material online at http://cjasn.asnjournals.org/lookup/suppl doi:10.2215/CJN.07010618/-/DCSupplemental.

Supplemental Table 1. Clinical characteristics of 500 patients undergoing hemodialysis with a history of catheter access.

References

Received: June 11, 2018 Accepted: January 3, 2019

Published online ahead of print. Publication date available at www.cjasn.org.