Hemodialysis Central Venous Catheters as a Source of Inflammation and Its Implications

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ABSTRACT

The mortality rate for end-stage renal disease patients is six times higher than in the general population. Hemodialysis central venous catheter (CVC) utilization has increased by 50% between 1998 and 2004 and data from the United States Renal Data System suggest that 81% of the patients initiate hemodialysis through a CVC. There is evidence that the two observations are linked in both an obvious way (catheter-related sepsis) as well as in a less obvious manner—chronic inflammation. Inflammation is highly prevalent in chronic hemodialysis (CHD) patients and is consistently associated with poor outcomes. Some of the most important consequences of inflammation in CHD include, but are not limited to, cardiovascular disease, uremic protein-energy wasting, erythropoietin hyporesponsiveness, and increased hospitalization and death rates. Use of CVC has been long suspected to play a role in the inflammatory response in CHD patients. Recent studies have shown that the presence of CVCs is associated with higher levels of C-reactive protein (CRP), lower serum albumin values, and lower hemoglobin values. Furthermore, there are data showing that CRP levels decrease following CVC removal. Accordingly, avoidance of CVC represents an effective strategy to limit the inflammatory response in CHD patients and potentially prevent its devastating consequences.

Mortality rates for end-stage renal disease (ESRD) patients remain unacceptably high (1). Among ESRD patients 65 years of age or older, mortality rates are six times higher than in the general population. The lack of progress in lowering hemodialysis mortality rates is concerning, and raises the question of practices that may adversely affect mortality. One of the most compelling is the high utilization of central venous catheters (CVCs) which has seen a rampant increase in the United States (1).

Data from the United States Renal Data System (USRDS) show that CVC placement rate in incident chronic hemodialysis (CHD) patients has increased by 50% between 1998 and 2004. Medicare medical evidence forms for 2005 showed that 81% of incident CHD patients received their first outpatient dialysis session through a CVC and that only 26% of those had an arteriovenous fistula (AVF) or a polytetrafluoroethylene graft placed prior to initiation of CHD (Fig. 1). The reasons for high CVC utilization are multiple, including late referral, older age (patients older than 65 have a lower AVF placement rate), gender (women have a lower AVF placement rate), the lack of pre-ESRD coverage, and certain practice patterns. There is also a concern that this trend may have been an undesired consequence of the implementation of the Fistula First program (2).

Hemodialysis Catheter as a Source of Inflammation

Inflammation is highly prevalent and persistent in the CHD population, with the median C-reactive protein (CRP) concentration most commonly reported between 5 and 8 mg/l for different cohorts (3–6). While there is no current consensus regarding cutoff levels of CRP to define clinically relevant inflammation in ESRD patients, the prevalence of inflammation in CHD patients has been reported anywhere from 35% to 70% depending on the assay used and the cutoff value for CRP (3–8). We have recently reported our own observations in which we recorded monthly measurements of CRP in 128 prevalent CHD patients for a period of 2–26 months (median 12). In this study, 70% of the CHD patients had a median CRP greater than 3 mg/l. In any given month, the median CRP for the cohort was 5.7 mg/l and that 25% of the patients had a CRP of 16.2 mg/l or greater (severely inflamed) (7).

Inflammation in CHD patients is multifactorial (Fig. 2). There have been very few studies evaluating the contribution of CVC to the inflammatory response of
ESRD. Movilli et al. completed a small cross-sectional study in which they showed that the median CRP for patients with CVCs ($n = 13$) was 20 mg/l vs. 5 mg/l for patients with AVFs ($n = 48$, $p < 0.0001$) (9). Similar results have been reported in abstract form by Harbord et al. who performed a cross-sectional study examining the association of access type and inflammation in 27 CHD patients and showed that IL-1b, IL-6, and hsCRP were statistically significantly higher in nine CVC patients versus nine AVF patients (10). Goldstein et al., again in abstract form, reported similar results of a cross-sectional study in 118 adult prevalent HD patients looking into the association between access type (AVF, AVG, CVC) and CRP. In the same study, it was reported that in a small longitudinal cohort of 35 incident CHD patients, CRP decreased over 6 months once CVC was changed to an AVF as the permanent access. In addition, 6 months after changing from CVC to AVF, 35 patients had reduced weekly EPO dose ($13,425 \pm 225$ to $5875 \pm 175$ units, $p < 0.01$), increased serum albumin levels ($3.2 \pm 0.4$ to $3.8 \pm 0.2$ g/dl, $p < 0.05$) and increased hemoglobin concentrations ($10.3 \pm 1.6$ to $12.2 \pm 1.2$ g/dl, $p < 0.03$) (11).

In our longitudinal cohort of 128 patients, HD catheter use was an independent and robust predictor of the inflammatory response after adjusting for relevant confounders ($\beta = 5.28$, $p = 0.002$). Furthermore, we were able to show (Fig. 3) both an increase in CRP concentrations with catheter insertion ($n = 17$, 7.5-fold increase in the CRP concentration) and a drop in the CRP concentrations following catheter removal ($n = 14$, 59% drop in the CRP concentration) (7).

Consequences of Inflammatory Response in CHD Patients

Cardiovascular Disease (CVD)

It has been estimated that despite stratifying for age, gender, and race, CV mortality is 10–20 times higher in ESRD patients compared with the general population. Despite this large burden of CVD in the ESRD population, the traditional CV risk factors alone do not account for all the increased CV risk in CHD patients (12–15). Accordingly, recent studies focus more on nontraditional risk factors such as inflammation, oxidative stress, endothelial dysfunction, and vascular calcifications. Biomarkers of inflammation have consistently predicted CV risk, and CV mortality in CHD (5,6,16). It is important to underscore that inflammation is highly interrelated to other nontraditional CV risk factors (4).

Several studies have shown that CVCs are associated with all-cause (17–21), cardiovascular (18,19), and infectious mortality. A prospective study using the USRDS wave 1 cohort (a random sample of 5507 prevalent CHD patients with and without diabetes mellitus, DM) evaluated the correlation of the type of access and cause-specific mortality. They reported that death caused by cardiac causes was higher in CVC than in AVF for both DM (RR 1.47, $p < 0.05$) and non-DM (RR = 1.34, $p < 0.05$) (18).

The mechanisms by which CVCs lead to increased CVD and CV death are not well defined. However, it is speculated that there are two possible...
mechanisms—directly through chronic inflammation (foreign body) or indirectly through the known increased risk of septicemia and bacteremia which generates peaks of high inflammation. For example, Ishani et al., using a prospective cohort of incident dialysis patients from theUSRDS wave II, reported that CVC was the most important factor in the subsequent risk of septicemia and bacteremia, which are important risk factors for cardiovascular events and death. The link of peak of inflammation (infectious episode) with the subsequent risk of cardiovascular events has been also shown in the general population (19).

Infectious Episodes

One of the interrelated mechanisms by which catheters contribute to inflammation and subsequently adverse outcomes in CHD patients is infectious episodes. The most concerning aspect of catheter use is a high infection rate, estimated at 2.5–5.5 cases/1000 patient-days or 0.9–2.0 episodes/patient-year. For most patients, the question is not “if,” but “when” bacteremia will occur if catheters are maintained indefinitely. Once bacteria proliferate in the bloodstream, satellite foci of infection can occur via hematogenous spread, predisposing patients to endocarditis (22), vertebral osteomyelitis (23,24), septic pulmonary emboli/abscesses (25,26), and meningitis (27). Underlying immune dysfunction predisposes to sepsis (28,29), increasing death risk 5-fold to 9-fold. Obviously, a high systemic inflammatory response is associated with the infectious episode, and can be considered as either a marker or a significant contributor to the adverse consequences of the infectious episode, mostly through the acute release of pro-inflammatory cytokines and acute phase reactants.

Uremic Protein Energy Wasting

Although an anorexia/poor appetite is a common complication of advanced kidney disease (30), the “malnutrition” found in the majority of CHD patients resembles that of a state of cachectic syndrome seen in conditions with persistent inflammation (30–33), such as cancer cachexia, congestive heart failure, AIDS, and tuberculosis, which are characterized mainly by muscle wasting. Inflammation can lead to muscle wasting through multiple mechanisms, including activation of the ATP-ubiquitin-proteasome pathway, insulin resistance, hypermetabolism, hormonal derangements such as resistance to anabolic hormones, and decreased appetite. Isolated interventions in the form of nutritional energy and protein supplementation have been proved to be effective in improving nutritional status and outcome in ESRD patients in most, but not in all, patients, presumably because of the need to attack other causative factors like inflammation (33). Accordingly, interventions modulating the inflammatory state might represent intriguing strategies to improve the nutritional state in ESRD patients.

Human Recombinant Erythropoietin (rHuEPO) Hypo-responsiveness

Anemia of CKD has been a focus of much attention as a potential contributor to poor quality of life, CVD and mortality in ESRD patients. Despite the administration of rHuEPO, a significant percentage of ESRD patients still do not achieve hemoglobin targets recommended by international guidelines (34). This condition has been termed EPO hypo-responsiveness and refers to the inability to achieve hemoglobin greater than or equal to 11 g/l despite having appropriate storage iron and rHuEPO doses in excess of 500 IU/kg/week (per KDOQI-2006 guidelines) (35) or in excess of 300 IU/kg/week (as per the European Best Practices guidelines) (36). Several factors have been implicated in the hypo-responsive-ness to rHuEPO, with inflammation being an important one.

Inflammation appears to influence rHuEPO response through at least two mechanisms. First, pro-inflammatory cytokines such as tumor necrosis factor-α (TNF-α), interferon-γ, and interleukin-1 directly inhibit the differentiation and proliferation of erythroid progenitor cells (4,37–43). The second mechanism is through the disruption of iron metabolism; interleukin-6 stimulates the hepatic expression of hepcidin, a liver-derived peptide that plays a pivotal role in the regulation of iron homeostasis, by inhibiting duodenal absorption of iron and the release of iron from macrophages and hepatocytes. Data indicate that hepcidin-mediated hypoferremia occurs shortly after interleukin-6 production increases (41,43,44). Further, TNF-α, interleukin-1, interleukin-6, and interleukin-10 induce ferritin expression and stimulate the storage and retention of iron within macrophages. Additionally TNF-α and interferon-γ inhibit the production of erythropoietin in the kidney, and decrease the life span of red cells. Despite this intriguing link, studies examining the treatment of the underlying inflammation and its impact on EPO responsiveness are scarce, but obviously are needed.
Inflammation is potentially the basis for many of the devastating complications seen in the CHD population. CVCs are clearly a modifiable source of inflammation. Given that there are no current effective treatments for chronic inflammation in ESRD or its consequences, the focus must be on prevention. The literature is already replete with admonitions regarding the excessive use of CVCs. To that chorus, we add our voice by highlighting both the subtle inflammatory effects of CVCs (from foreign body effects and biofilm) as well as the well-recognized dramatic, acute inflammation seen with catheter-related bacteremia and sepsis.

References

12. Foley RN: Cardiac disease in chronic uremia: can it explain the reverse epidemiology of hypertension and survival in dialysis patients? Semin Dial 17:275–278, 2004