

“Hiding In Plain Sight”

Chronic Kidney Disease and Potential Consequences of the Proinflammatory State Hemodialysis Catheter-Related Masses

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Abstract

Multiple observational and experimental data support that chronic kidney disease (CKD) represents a “proinflammatory” state. These findings link this disordered inflammation and immunity to increased adverse cardiovascular (CV) events present in CKD through their role in atherosclerosis, but mechanisms of activation, recruitment and propagation remain unclear. Accordingly, the present effort reviewed the common use of indwelling hemodialysis catheters as a potential inflammatory trigger and immuno-amplifying variable. Hemodialysis intravenous catheters are routinely used to provide essential functional vascular access for patients requiring emergent or urgent hemodialysis. Numerous observations report that even within hours to days after insertion, a fibrin-thrombin-cellular matrix often forms around the catheter. This catheter associated “biomass” is so common it is usually thought to be clinically silent. But intravenous masses attached, or sheared off at catheter removal or remaining even after catheter explantation are recognized to provoke embolic and direct hemodynamic-related injury. Perhaps less recognized is that their formation, size and growth may be mechanistically linked to the heightened vascular immuno-reactivity found in CKD. Thus, vascular catheter placement or the associated reactive fibrin-thrombin-cellular matrix (or both) may directly contribute to pathologic CV immune-responsiveness in hemodialysis patients.

Introduction

It is now hypothesized that chronic kidney disease (CKD) represents a “proinflammatory” state.^[1,2] Evidence from both experimental and clinical reports support the role of inflammation and immunity in atherosclerosis accounting for increased cardiovascular (CV) related mortality.^[3] Complete understanding of the mechanisms of immune/inflammatory activation, recruitment and propagation remain unclear. However, collectively CV outcomes noted in CKD are linked to both systemic and local pathologic dysregulation.^[4-7] Published data reveal that formation and enlargement of a plaque is a nuanced interplay between resident vascular smooth muscle cells and multiple immuno-reactive cell populations.^[4] This unfolding biological narrative involves specific protein signals from unique T-cells within the atheroma, along with mononuclear, and macrophage contributors to initiate, expand and morphologically shape the plaque that will become clinically expressed as coronary artery disease.^[5,8-13] In addition, it is evident that the involved cellular-based immunologic processes can also moderate the phenotypic outcome of a typical plaque. Essentially, it represents modulation of these processes to repair or mitigate potential injury.^[12,14] Thus, it appears that this complex immunoinflammatory interplay, often in the form of apocrine and/or autocrine communication, is involved in both atheromatous and arterial morphogenesis, connecting each to subsequent altered vascular outcomes.^[12]

Inflammation intrinsic to catheter use?

We wish to comment upon the common and often indispensable practice of using indwelling venous catheters to provide essential functional vascular access for patients requiring emergent or urgent hemodialysis. In this setting, hemodialysis is mandated with time-sensitive vascular access most frequently accomplished via a two-port intravenous hemodialysis catheter allowing adequate flow rates to ensure effective hemodialysis.^[15] It is often indicated for volume overload, life-threatening electrolyte abnormalities, acidosis or manifestations of uremia.^[15-18] Additionally, a frequently encountered clinical challenge occurs when patients experience chronic renal injury requiring hemodialysis in the setting of limited vascular access.^[19] Catheter use in this setting is a practical necessity and occurs for variable intervals. Current literature details the many clinical issues encountered when hemodialysis is performed through use of venous catheters.^[20-30] These include up to a seven-fold increase in rates of infection compared with surgically created arteriovenous (AV) fistulas and increased catheter-related thrombotic burden limiting flow rates and creating an embolic potential.^[21,26,27] Although their practical long-term use is limited by these potential complications, real world utilization of hemodialysis catheters may be extended for significant intervals of time.^[15]

Numerous observations report that even within hours to days after insertion, a fibrin-thrombin-cellular matrix often forms around the catheter.^[31-48] This catheter-associated “biomass” is common and is

usually thought to be clinically silent. But when sheared off at catheter removal (Figures 1 & 2) their residua may provoke embolic and direct hemodynamic-related injury.^[35,37,40-45,48] Subsequent echocardiographic identification of these catheter-attached fibrin-thrombin-cellular matrices or biomasses are well described. They have been identified in the subclavian vein, right atrium, superior vena cava, (Figures 1 & 2), inferior vena cava (IVC) or right ventricle (RV). An astute echocardiographer will frequently infer their presence and related etiology to a current or recently removed catheter.^[49] But beyond this more obvious hemodynamic and anatomic injury potential exists a more nuanced concern of inherent catheter-related inflammatory pathobiology. First, catheters themselves may trigger local or even systemic inflammation that could lay the groundwork for adverse vascular and CV outcomes.^[50,51] And second, catheter associated biomass formation, size and rates of growth may reflect or even amplify vascular immuno-reactivity found in CKD.^[46,52-55]



Figure 1: This thick-walled encasement on the longitudinal axis (Figure 1), showed the central echolucent lumen likely formed around the external surface of the catheter. The distal end of the remnant cast is also striking for the multiple filamentous extensions. The biomass is in the superior vena cava and extends into the right atrium.



Figure 2: Same patient cross sectional short axis (Figure 2), showed the central circular lumen formed around the external surface of the catheter. The biomass is in the superior vena cava and extends into the right atrium.

Different but converging lines of evidence hint that catheters themselves may trigger downstream biologic responses not fully appreciated but perhaps important contributors to immunoinflammatory dysregulation.^[46,53-56] For many years nephrologists have observed that albumin levels inversely correlate with hemodialysis catheter use and may result from heightened inflammation.^[51,56] In fact, implanting a dialysis catheter has been demonstrated to be significantly correlated to higher C-reactive protein levels, while after catheter removal, these elevations return to baseline levels.^[51,56] These results suggest that the presence of a hemodialysis catheter is an independent determinant of an exaggerated inflammatory response in CKD requiring hemodialysis. Alternatively, these higher C-reactive protein levels could reflect the spectrum of disparate etiologies of pre-existing CKD, independent of catheter use. Regardless, these data have required reexamination of long-held views that previously regarded catheter use as innocuous. The subtle and often unforeseen cellular communication directly related to immunoinflammatory stress within the vascular microenvironment may have profound effects.

Other Sources of Immunoinflammatory Injury

Newly observed findings demonstrate that local bacterial infections generate inflammatory stress and cause responses in “distant” vascular territories.^[57] Thus, diabetic foot infections or pneumonia may initiate and amplify remote immunoinflammatory responses in native vascular or immunoactive cells geographically removed from the initial infection.^[57,58] This has been termed an “echo” effect and supports the observation that pneumonia is linked to increased thrombotic and adverse cardiovascular outcomes.^[12] Experimental data further support that localized inflammatory responses to systemic bacterial endotoxin can activate a more reactive inflammatory biochemical profile in atherosclerotic arteries than in normal arteries.^[57] This may hint at a responsible mechanism whereby periodontal or gram-negative bacteria are associated with increased CV ischemic outcomes.^[59] It is thus tempting to assign any inflammatory perturbation as a likely contributing element in the adverse cardiac atheromatous-based outcomes observed in CKD.

Catheter use in hemodialysis provides fertile ground for vascular bacterial release.^[27,29,59] But implicating catheter use as the sole or even critical proximate cause for immunoinflammatory vascular atheromatous damage in patients with CKD is almost certainly an oversimplification. Patients requiring hemodialysis present with an etiologic spectrum of end stage CKD, accompanied by multiple comorbidities each contributing to their CKD etiology and phenotype. These factors likely underwrite the “proinflammatory” state found in CKD, perhaps independently of subsequent modes of hemodialysis. Gastrointestinal microflora may also be an important contributor, potentially providing a diverse source of bacterial products including endotoxins and heat-shock proteins that may cross epithelial barriers and generate local and systemic inflammatory injury.^[60,61] Recent speculation has hypothesized that microbial pathogen associated molecular patterns (PAMPs), small molecular motifs conserved within a class of microbes, can activate innate immune receptors.^[62,63] These conserved molecular motifs are found within bacterial lipopolysaccharides, endotoxins located on the cell membranes of gram-negative bacteria, flagellum and lipoteichoic acid from gram-positive bacteria.^[64,65] When these PAMPs activate cellular immunity through toll-like receptors

(TLRs), formyl-peptide receptors (FPRs) or C-type lectin receptors (CLRs), and Nod-like receptors (NLRs) for example, they are hypothesized to be responsible for leukocyte and vascular cell activation within atheromata.^[63,66,67] These pathways then may facilitate the linkage between the heightened inflammatory state in CKD and the significant cardiovascular mortality.

Thus, data support that altered immunoinflammatory activity in patients undergoing hemodialysis likely contributes to vascular injury. It may indeed be mechanistically related to adverse cardiac outcomes, however little is known about a potential connection between the CKD proinflammatory state and catheter-associated biomasses. It is also unclear whether the appearance, extent and time course of these biomasses have any contributory role in further immune perturbation. But given the proinflammatory state existing in CKD and the central role of altered immunoinflammatory expression impacting CV outcomes, it may no longer be reasonable to dismiss these catheter-attachments as completely innocent. Once the catheter is introduced into the vein, it may serve as a “trip wire” in effect to boost both the local and perhaps also the systemic pre-existing inflammatory cascade initiating a chain of events that initially targets the catheter. But in doing so, it may also confer foreseeable harm to collateral or downstream structures. It may even accelerate atheromata plasticity, contributing to ischemic CV outcomes known to plague patients with CKD on dialysis.

Additional Intravascular Concerns

But beyond catheter use and its potential linkage to CV events through immunoinflammatory-mediated sequelae, this paradigm may extend to other clinical therapeutics. In spite of increasingly judicious use, indwelling IVC filters subsume a growing list of well-defined complications.^[68-71] Again, these comprise reported hemodynamic and embolic events, the latter composed of both thrombotic and structural device-related injury. But much less is known about the immunoinflammatory consequences of even temporary intravenous use. Combining a vulnerable vascular environment found after trauma or embolic injury with the inherent properties of an IVC filter may challenge human bio-immunology in ways not readily foreseeable.

Another example of potential intravenous inflammatory activation is related to pacemaker lead placement.^[72] Here only short-term data have been gathered and are believed to be secondary to local minor injury associated with implantation.^[72] But, similar to hemodialysis catheters, there are frequently fibrotic attachments to venous, valvular and cardiac structures representing immunoinflammatory reaction to their presence.^[73] Collectively, these indwelling intravascular objects may trigger or amplify potentially important molecular and cellular communication, forming the biological infrastructure of immunoinflammatory dysregulation.

Finally, the thrombotic and embolic complications associated with indwelling hemodialysis catheters and other intravascular therapeutic modalities are commonly identified in both case reports and prospective analysis. For hemodialysis catheters, this is among the most obvious set of concerns and as noted previously, is part of the narrative of their foreseeable injury potential. Nevertheless, the cumulative impact may still be underappreciated.^[74,75] This is of interest because pulmonary hypertension (PH) in hemodialysis

patients is unexpectedly frequent and thought to have a multifactorial etiology. This includes high cardiac output, anemia and fluid overload coupled with chronic left ventricular pathology.^[75-77] But there is also ongoing interest in the potential contribution of venous hemodialysis catheters and their residual fibrin/thrombin remnants having a role in pulmonary vascular injury and subsequent PH.^[78-82]

Repetitive pulmonary vascular injury and subsequent elevated pulmonary pressures may be a consequence of catheter-related biomass volume and its inflammatory sequelae.^[78] As noted, a variety of mechanisms may be involved in what is now generally reported to be a proinflammatory environment especially vulnerable to venous thromboembolic events.^[1,2,78] The critical variables of this “perfect storm” in CKD remain speculative and largely unstudied, but the spectrum of pathology is tangible. Our concern is that catheter-related fibrin/thrombotic biomass volume in this environment cannot be ignored or treated as innocuous. These concerns may also apply to other intravenous “therapeutics”, such as the afore mentioned IVC filters, in that beyond the often predictable injury secondary to thrombotic emboli is the potentially longer lasting and indeed undefined immunoinflammatory dysregulation that may add to the vascular remodeling including PH.

Conclusion

Different observational and experimental data support that chronic kidney disease (CKD) represents a “proinflammatory” state. Such disordered inflammation and immunity may indeed be linked to increased adverse CV events present in CKD. Their role in the pathobiology of atherosclerosis is becoming more obvious but detailed mechanisms that modulate clinical expression remain unclear. The present effort put forth a hypothesis that indwelling hemodialysis catheters may act as an inflammatory trigger or immuno-amplifying variable. These intravenous catheters are important therapeutic agents as they are used to provide essential functional vascular access for patients requiring emergent or urgent hemodialysis. But numerous observational reports have shown fibrin-thrombin-cellular matrices commonly form around hemodialysis catheters. While such biomasses may be attached, sheared off at catheter removal or remain even after catheter explantation, they are recognized to provoke embolic and direct hemodynamic-related injury. However, of greater interest is that their formation, size and growth may be mechanistically linked to the heightened vascular immuno-reactivity found in CKD and this concern remains largely unexplored. Catheter-related biomass and/or residua must be accounted for and further investigated if we are to improve overall safety of catheter use in this vulnerable population.

Declarations

This manuscript has met specific criteria for institutional ethical approval and consent to publish.

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