Vasculature and Kidney Complications in Sickle Cell Disease

Karl A. Nath* and Zvonimir S. Katusic†

*Division of Nephrology and Hypertension, Internal Medicine, Department of Physiology and Biomedical Engineering; and †Departments of Anesthesiology, Molecular Pharmacology, and Experimental Therapeutics, Mayo Clinic, Rochester, Minnesota

ABSTRACT

Recent developments in sickle cell disease include the concept of a vasculopathic state and the classification of sickle cell disease into a hemolysis-endothelial dysfunction phenotype or a viscosity-vasoocclusion phenotype. The hemolysis-endothelial dysfunction phenotype largely reflects deficiency of or resistance to nitric oxide. In addition to discussing these areas, we suggest that the hemolysis-endothelial dysfunction phenotype also reflects the instability of sickle hemoglobin, the release of heme, and the induction of heme oxygenase-1. From these perspectives the renal complications of sickle cell disease are discussed and classified.


A century ago, James Herrick described sickle-shaped red blood cells (RBCs) in a West Indian dental student presenting with fever, leg ulcers, and respiratory symptoms.1 This misshaping of RBCs not only named the condition as sickle cell disease (SCD) and gave it an icon, but has long been regarded as a fundamental contributor to vasoocclusive disease: sickle RBCs, compromised rheologically because of polymerization of sickle hemoglobin, create a vascular logjam, thereby leading to vasoocclusion.

SCD is now recognized as involving not just vasoocclusion but also a plethora of pathogenic processes categorized under the following rubrics: ischemia-reperfusion injury, inflammation, hemolysis, a procoagulant state, oxidative stress, nitric oxide (NO) deficiency, endothelial activation, aberrant vascular reactivity, and sympathetic-parasympathetic imbalance.2–4 These processes broadly interact, and any one may be influenced by others. A challenging issue is understanding the hierarchical construct that integrates these myriad pathways, linking them back to the aberrant behavior of sickle hemoglobin, and appraising their relative importance in SCD.

VASCULOPATHY IN SCD

Studies by us and others more than a decade ago demonstrated the existence of endothelial dysfunction in murine models of SCD, a finding also observed in human SCD.5,6 These observations were a prelude to the concept of SCD as a vasculopathic disease,2 a perspective now widely accepted for the following reasons:4,7–9 It identifies a nexus for all other pathogenetic pathways; it helps explain the clinical manifestations of SCD, especially pulmonary hypertension, priapism, leg ulcers, and stroke (complications that may be associated with vascular histologic lesions); and it emphasizes the role of the interface between circulating blood and resident tissue in mediating disease, one to which therapies may be directed.

Classic risk factors for vascular disease—specifically, hypercholesterolemia, hyperlipidemia, hyperglycemia, and hypertension—cannot explain the development of vasculopathy in SCD.2,7,8 Patients with SCD do, however, exhibit systemic inflammation: Plasma levels of diverse inflammation-related molecules (IL-1, IL-8, monocyte chemoattractant protein-1, TNF-α, and endothelin-1) are elevated, whereas circulating leukocytes are increased and activated, and predict morbidity in SCD. Such an inflammatory milieu promotes endothelial activation, which can instigate inflammatory and procoagulant processes in the vasculature leading to vasculopathy. The procoagulant setting of SCD may also predispose to vasculopathy, and such molecules as tissue factor and plasminogen activator inhibitor-1, which are both procoagulant and proinflammatory, are substantially upregulated.

Endothelial generation of NO in the healthy vasculature exerts vasorelaxant, anti-inflammatory, and antithrombotic effects, and thus deficiency of or resistance
to NO that occurs in SCD may underlie the vasculopathy.3,4,7–9 Deficiency of NO may be due to the following: NO scavenging by the heme group of sickle hemoglobin released into plasma by lysed RBCs; NO scavenging by vascular superoxide anion; depletion of plasma arginine by arginase released by lysed RBCs; and the effect of endogenous NOS inhibitors. Oxidative stress in SCD also inactivates tetrahydrobiopterin, a NOS cofactor, thereby uncoupling endothelial NO synthase such that superoxide anion, rather than NO, is produced. In certain settings vascular reactivity to NO is blunted.3,5

NO deficiency is a salient consideration in the classification of SCD into the hemolysis-endothelial dysfunction or the viscosity-vasoocclusion phenotypes.4,7–9 Such a distinction draws on the clinical observation that chronic organ injury in SCD may not correlate with vasoocclusive disease and emphasizes the increased likelihood of a vasculopathy occurring in the hemolysis-endothelial dysfunction phenotype.

Vasculopathies are manifest not only structurally but also functionally, and vascular behavior in SCD is abnormal in several ways.3 First, in contrast to the hypoperfusion of vasooccluded microcirculatory beds, hyperperfusion occurs in the systemic circulation in SCD: Systemic vascular resistances are decreased, cardiac output is increased, and there is enhanced perfusion in certain organs, particularly the kidneys, and in certain regional beds, such as the forearm. Indeed, patients with SCD without CKD exhibit lower systemic BP than healthy controls.

Second, certain vascular beds in steady state exhibit an upregulation of both vasoconstrictor and vasodilator species whose countervailing actions determine net perfusion; vasodilator systems, already upregulated in steady state, may not adequately counter additional vasoconstrictive stress during painful episodes, thereby incurring vascular instability.3

Third, in several settings, the vascular in SCD exhibits increased sensitivity to vasoconstrictor species, including α1-adrenergic agonists10 and endothelin-1.11 Finally, SCD exhibits an abnormal response to shear stress.6,12 Shear stress is a fundamental determinant of vascular behavior: High laminar shear stress is vasoprotective by promoting the endothelial generation of NO, in part through the transcription factor KLF2; low laminar and oscillatory shear stresses are vasopathologic through proinflammatory transcription factors. We have recently demonstrated that there is an exaggerated response to vasopathologic shear stress in a murine model of SCD,12 whereas clinical observations in human SCD demonstrate impaired responses to shear stress and suggest that decreased KLF2 expression correlates with an increased risk for stroke in SCD.13

### VASCULATURE AND KIDNEY DISEASE IN SCD

Patients with SCD exhibit recurrent episodes of hematuria and tubular abnormalities, such as a concentrating defect. Some 70% of patients may exhibit microalbuminuria, and 26% of adult patients develop CKD, the latter increased with aging.14–16 Of interest, the prevalence of sickle trait is high in African-American patients undergoing renal replacement therapy.17

These manifestations may reflect an abnormality in vascular perfusion or behavior. For example, recurrent bouts of hematuria and tubular dysfunction arise from medullary ischemia due to sludging of RBCs in the vasa recta; such sludging occurs because of hypoxia, hypertonicity, and acidosis in the medullary environment, along with its relatively low blood flow.

In contrast to hyperperfusion of the medulla, in SCD the cortex is often hyperperfused because of decreased renal vascular resistance. This increased blood flow is attended by increased GFR. Hyperperfusion of the kidney promotes glomerulomegaly, the latter, in certain settings, presaging glomerulosclerosis.18 Glomerulosclerosis, the most common glomerular pathology in SCD, also probably reflects hemodynamically mediated glomerular damage by hyperfiltration; hyperfiltration is a risk factor for proteinuria and CKD in SCD. Furthermore, hyperfiltration increases the filtered sodium load and tubular reabsorption of sodium, thereby augmenting renal oxygen consumption. Such hypermetabolism promotes tubulointerstitial injury through oxidative stress and other mechanisms.19 This effect could prove particularly damaging when there are increased renal deposits of iron, as occurs in SCD.

Hemolysis is also a risk factor for hyperfiltration, proteinuria, and CKD in SCD,20–23 and complications of SCD, such as pulmonary hypertension, which are strongly associated with hemolysis and vasculopathy, are risk factors for CKD.24,25 That hemolysis is associated with hyperfiltration seems quite puzzling because hemolysis commonly induces a renal vasoconstrictive state (NO scavenging by hemoglobin), whereas hyperfiltration is often attended by hyperperfusion in SCD.

We propose that in SCD, hemolysis per se can induce vasodilation, either regionally or systemically, because of the unstable nature of sickle hemoglobin. Such instability leads to the release of heme and the induction of heme oxygenase-1, the latter exerting vasorelaxant effects through the generation of carbon monoxide and oxidant-scavenging actions. In support of this are prior studies demonstrating increased plasma levels of heme in SCD26 and our observations that heme oxygenase-1 is robustly induced in the endothelium and smooth muscle cells in renal arteries in human SCD.27 Heme itself is proinflammatory, inducing, for example, the vasculopathic chemokine, monocyte chemoattractant protein-1,28,29 and may thus promote vascular injury.28–30 Finally, the trafficking of heme across the glomerular filtration barrier exposes the endothelia and podocytes to a metabolite with cytotoxic and proapoptotic effects,28,31 thereby impairing glomerular permselectivity and causing proteinuria.

On the basis of these considerations, Figure 1 expands the hemolysis-endothelial dysfunction phenotype in the kidney to...
include the downstream effects resulting from the release of heme from sickle hemoglobin, and Table 1 categorizes the kidney complications of SCD according to this modified classification.

The viscosity-vasoocclusive phenotype, normally confined to the medulla, may extend into the cortex after renal stress, and such extension is accompanied by pronounced reductions in renal blood flow and GFR.\textsuperscript{32,33} That such extension also occurs in human SCD is supported by the occurrence of acute kidney injury during intercurrent illnesses in patients with SCD,\textsuperscript{34} reductions in renal blood flow during painful episodes,\textsuperscript{35} and histologic documentation of cortical vascular congestion in patients with SCD who have acute kidney injury.\textsuperscript{36,37}

**CONCLUSIONS**

SCD is a chronic disease punctuated by acute insults that target, among others, the vasculature and its endothelium; SCD is also characterized by adverse, long-range signaling to distant organs and tissues from seemingly contained insults. Both considerations are relevant to the kidney in SCD.

As is now clear from studies of acute kidney injury, renal ischemia induces renal endothelial cell loss and endothelial-mesenchymal transition, effects that contribute to the increased risk for CKD after ischemic acute kidney injury.\textsuperscript{38} We suggest that episodic injury to the glomerular and cortical capillaries, caused by vasoocclusive and other insults, may contribute to CKD in SCD.

Events originating elsewhere in patients with SCD can target the kidney, and the kidney, in turn, can engage in long-range signaling to distant organs and tissues. Ischemia localized to one kidney, for example, can induce glomerular and cortical capillary congestion in the intact, contralateral kidney, and ischemia localized to both kidneys can induce vascular congestion and sickling in pulmonary capillaries.\textsuperscript{32} Such action-at-a-distance of kidney injury in SCD, channeled through the vasculature, may thereby contribute to the morbidity of SCD.

**ACKNOWLEDGMENTS**

We thank Tammy Engel for her secretarial expertise.

These studies were supported by National Institutes of Health Grants DK47060, HL-55552, and HL-91867.

**DISCLOSURES**

None.

**REFERENCES**

1. Herrick JB: Peculiar elongated and sickle-shaped red blood corpuscles in a case of...