Ischemia-reperfusion Injury in Sickle Cell Anemia

Relationship to Acute Chest Syndrome, Endothelial Dysfunction, Arterial Vasculopathy, and Inflammatory Pain

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KEYWORDS

• Ischemia-reperfusion • Sickle • Endothelial dysfunction • Inflammation

KEY POINTS

Disparate clinical features and vascular biological abnormalities characteristic of sickle cell anemia can be explained readily by viewing this disease as an example of ischemia-reperfusion (I/R) injury, which establishes a chronic, systemic inflammatory state.

- In sickle I/R, the triggering ischemia probably occurs in the microvasculature and in a dispersed, multifocal manner.
- Features of sickle I/R are influenced by the multitude of modulating factors present in its uniquely complex milieu.
- Acute chest syndrome may be an example of I/R-induced remote organ injury.
- Other sickle disease features explainable by the I/R character of sickle disease include endothelial dysfunction with aberrant vasoregulation, large vessel vasculopathy, and inflammatory pain.

INTRODUCTION

Ischemia-reperfusion (I/R) physiology, also called reperfusion injury, is a fundamental vascular pathobiological paradigm, which instigates vascular and tissue injury in a variety of human disease states. This review describes why sickle cell anemia should be conceptualized in this fashion and how I/R physiology explains the genesis of characteristic aspects of vascular pathobiology and clinical disease in sickle cell anemia.

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For clarity, the nature of I/R generally is presented first, followed by an exposition of the relevance of this information to sickle cell anemia. The clinical complications to be emphasized are the acute chest syndrome (ACS), endothelial dysfunction with aberrant vasoregulation, circle of Willis vasculopathy, and inflammatory pain. Viewing sickle disease from this perspective elucidates defining pathophysiology and identifies a host of novel potential therapeutic targets.

I/R INJURY

The basic concept of I/R is that tissue injury resulting from vascular occlusion occurs in 2 distinct phases. The first is direct ischemia-induced tissue injury or death, determined primarily by severity and duration of blood supply interruption. If occlusion resolves, allowing reperfusion of the previously ischemic area, the accompanying resupply of oxygen triggers a second, inflammatory phase. The latter establishes systemic inflammation and its sequelae, and sometimes results in remote organ injury (ROI) or even multiorgan dysfunction syndrome (MODS). This complex aspect of biomedicine is described by 2 reviews covering different decades of research using experimental animal models of I/R.[1,2] Additional citations are provided here when specific points require emphasis. This review emphasizes features that most clearly are specifically relevant to the sickle disease context.

Initiation of I/R

An occlusion causing ischemia triggers loss of adenosine triphosphate and reciprocal accumulation of hypoxanthine. This process is followed by cytosolic calcium accumulation, mitochondrial dysfunction, cell swelling, and cell death by inflammatory (necrosis) and noninflammatory (autophagy) mechanisms. In parallel, there is a dramatic change in xanthine dehydrogenase (XD), a widely distributed cellular enzyme that is particularly enriched in capillary endothelial cells, hepatocytes, and intestinal enterocytes. During hypoxia, XD is converted to its xanthine oxidase (XO) form, and significant amounts can be released into the blood space. Within minutes of restoration of reperfusion, XO begins using the accumulated hypoxanthine plus newly available oxygen to fuel superoxide radical generation. In turn, this process enables generation of other reactive oxygen species (ROS), events promoted by iron bioavailability. Thus, XO is understood to be largely responsible for the proximate burst of ROS that is believed to initiate the overall I/R process, resulting in I/R injury.[3]

The Further Evolution of I/R

Subsequent events rapidly become complex, with recruitment of an alarming panoply of cellular, vascular, and parenchymal cell processes that follow from I/R initiation. Additional sources of superoxide radical become activated. Blood-borne XO becomes associated with endothelial cell surfaces, thereby establishing superoxide generation at the endothelial surface. Activity of endothelial nicotinamide adenine dinucleotide phosphate (NADPH) oxidase increases, and endothelial dysfunction ensues with uncoupled endothelial nitric oxide synthase (eNOS) (see later discussion). Leukocytes become activated and generate oxidant. Other superoxide sources can contribute as well. Effects of ROS are indirect (caused by peroxide-based disruption of thiol redox status), modulatory (via effects on cell signaling), and damaging. Oxidant stress causes widespread and varied oxidative and nitrosative damage, which can adversely affect virtually all biological molecules.[4]

The ischemic area acquires multiple activated leukocyte types (polymorphonuclear neutrophils [PMN], monocytes, lymphocytes), dominated initially by PMN infiltration.