REVIEW ARTICLE

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Cardiovascular and Pulmonary Impact of the Ebola Virus: A Review of Current Literature and Practices

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EBOLA VIRUS DISEASE (EVD), caused by infection with the filovirus Zaire ebolavirus, has a wide range of cardiovascular and pulmonary effects. The disease was first observed in 1976 in the Ebola River valley in what is now the Democratic Republic of the Congo, Africa.[1] Since then, Zaire ebolavirus has caused a number of outbreaks over the past 3 decades[2] (Table 1) and has culminated in the current largest outbreak, which has spanned a number of West African countries and spread throughout the world (Table 2).[3]

The virus is transmitted via contact with mucosal surfaces, non-intact skin, or through injury with contaminated needles.[1] Following a 4-day to 10-day incubation period, the disease course includes fever, aches, malaise, severe vomiting and diarrhea, as well as increased vascular permeability, which leads to profound intravascular volume depletion.[1,4] While the hemorrhagic manifestations can be as minor as petechiae and bruising, the disease can progress to include gastrointestinal hemorrhage, subsequent shock, and multisystem organ dysfunction.[4] Swelling of the brain and kidneys can occur as well as necrosis of internal organs including the liver, testis, and ovaries.[5]

The recent outbreaks in Liberia, Guinea, Sierra Leone, and Nigeria have been the largest to date. Furthermore, with cases appearing in the United States and Europe, concerns have been raised about the possibility of even further spread abroad. This article seeks to review the knowledge of the vascular, cardiac, and pulmonary effects of EVD collected across medical specialties.

VASCULAR PATHOPHYSIOLOGY

The propensity of EVD to target endothelial cell lines is a hallmark of late disease. The initial target cells following exposure to EVD are dendritic cells and macrophages.[5,6] Subsequently, breakdown of endothelial cell barriers leads to the propensity for hemorrhage and fluid shifts among compartments (Fig 1).[1] Several mechanisms are thought to underlie this. First, EVD causes a systemic cytokine release that increases vascular permeability.[5] Furthermore, direct cytotoxic effects of EVD, particularly in later stages of infections, may contribute. Endothelial cells have been shown in vitro to support ebolavirus reproduction, and infected endothelial cells have been found in deceased patients.[5]

The ebolavirus glycoprotein (GP) may be of particular significance, both due to cytotoxicity and its role in facilitating endothelial cell rounding and detachment, worsening vascular leakage, and potentially hemorrhage.[1,5,6] Nitric oxide, a potent vasodilator, is found at elevated levels in infected patients and can contribute to shock.[5] In EVD, increased levels of tumor necrosis factor alpha also are found, which induces the expression of tissue factor on endothelial cells.[5] Disseminated intravascular coagulation may result, and inhibition of tumor necrosis factor in primates increases survival time in infected primates[5].

The course of EVD can include a marked hypovolemia secondary to fluid losses from diarrhea and vomiting, with intravascular volume depletion that is worsened due to extravasation of fluid. One report of a young, previously healthy patient demonstrated a pericardial effusion and a left pleural effusion on initial presentation.[7] The gastrointestinal tract was abnormal, with significant intraluminal fluid, decreased peristalsis, wall thickening, and hyperperfusion; the inability to absorb oral hydration in this state worsens hypovolemia.[7] Adrenal infection and necrosis may lead to a state of corticosteroid deficiency as well, with subsequent hypotension.[8]

CARDIAC PATHOPHYSIOLOGY

The effects of Zaire ebolavirus upon hemodynamic variables have been studied prospectively in Rhesus Macaques. Kortepeter et al showed that with onset of fever, 9 monkeys developed tachycardia with progressive hypotension, suggesting compensated shock.[9] As expected, these hemodynamic effects are mirrored in human patients with tachycardia that extended into a rate exceeding 140 beats per minute in historic reviews.[10]

With the recent outbreak of Zaire ebolavirus in West Africa, the treatment of patients in intensive care units in Europe and the USA has provided a unique level of documentation of the supportive care of infected patients in resource-rich regions. Similar hemodynamic responses to EVD are documented along with hemodynamic responses to high-dose vasopressors.[7]

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Table 1. Past Outbreaks

Year	Country	Cases	Deaths	Fatality Rate
2008	Democratic Republic of Congo	32	14	44%
2007	Democratic Republic of Congo	264	187	71%
2005	Congo	12	10	83%
2003	Congo	35	29	83%
2003	Congo	143	128	90%
2001-2002	Congo	59	44	75%
2001-2002	Gabon	65	53	82%
1996	South Africa (ex-Gabon)	1	1	100%
1996	Gabon	60	45	75%
1996	Gabon	31	21	68%
1995	Democratic Republic of Congo	315	254	81%
1994	Gabon	52	31	60%
1977	Democratic Republic of Congo	1	1	100%
1976	Democratic Republic of Congo	318	280	88%

Patients arrived to a biohazard containment unit at the University of Nebraska Medical Center with compensated volume depletion.[11] Orthostatic hypotension was present, but patients had normal heart rate and even potentially mild hypertension upon arrival. No laboratory evidence for adrenal insufficiency was present.

The decreased preload that previously is described can affect cardiac output. Systemic vascular resistance can markedly fall due to the systemic inflammatory response, with large numbers of circulating cytokines and nitric oxide. There can be decreased ventricular inotropy as well.[7] It is unclear if decreased contractility is a directly mediated effect from well-described cardiac cell invasion by Zaire ebolavirus, or secondary to electrolyte imbalances such as hypocalcemia.[12]

PULMONARY PATHOPHYSIOLOGY

The pulmonary clinical presentation of patients with EVD is often characterized by tachypnea, with potentially increased oxygen requirement.[10] Pulmonary failure can ensue, and patients have required supplemental oxygen and even mechanical ventilation. Dyspnea and respiratory compromise is a particularly poor prognostic sign in EVD, with an adjusted odds ratio of case fatality of 5.75 in a retrospective analysis.[13]

Patients at a biohazard containment center in the United States demonstrated tachypnea and an increased supplemental oxygen requirement.[11] The massive volume resuscitation required led to pulmonary congestion in 1 patient, with the need for diuresis. If mechanical ventilation is required, there is concern for ventilator contamination with the ebolavirus; appropriate filters are necessary, and the ventilator should be considered contaminated for 24 hours.[14]

One pathophysiologic effect of EVD is vascular leakage, which can lead to subsequent pulmonary edema.[7] The underlying cause of the vascular leak may be a combination of systemic cytokine release and direct endothelial cell infection.[7] Another cause of impaired oxygenation and ventilation is volume overload, particularly in the setting of renal failure. Measurements of extravascular lung water have been utilized to attempt to quantify the degree of vascular leakage into the pulmonary space.[7]

The lung tissue affected by EVD reveals alveolar edema, hemorrhage, and congestion.[12] Viral antigens are found within alveolar macrophages, endothelial cells, and fibroblasts as evidenced by immunohistochemical staining.[12]

LABORATORY ABNORMALITIES

Electrolyte abnormalities are expected given the magnitude of fluid losses and shifts, and subsequent cardiovascular effects must be expected and monitored. Hyponatremia, hypokalemia, hypomagnesemia, and hypocalcemia have been demonstrated even in early EVD.[7] A lactic acidosis from hypoperfusion and hypovolemia may combine with a non-anion gap metabolic acidosis from diarrhea to present an arterial blood gas consistent with a metabolic acidemia due to mixed causes.[15] Patients with EVD in the United States have required significant amounts of potassium, magnesium, and phosphate repletion.[11] Total parenteral nutrition has been administered with success when patient emesis ruled out the enteral route.[11]

Thromboyctopenia, anemia, and abnormal hepatocyte integrity and liver synthetic function tests also have been observed.[7] The thrombocytopenia probably is due to a consumptive coagulopathy, while hemoglobin concentration is more difficult to interpret. In EVD, the hemoglobin is affected not only by blood loss but also by volume status, and increasing hemoglobin concentration has been observed due to hemoconcentration. As disseminated intravascular coagulation progresses, abnormalities may worsen profoundly, which unfortunately prognosticate poorly. Hemorrhage had an adjusted odds ratio of mortality of 3.52 in a retrospective analysis.[13]

Increased serum levels of nitric oxide have been shown in the Sudan ebolavirus strain.[16] The degree of nitric oxide increase was markedly worse in patients who ultimately succumbed to their illness and reached peak levels at the time of death. The increase in nitric oxide is thought to be associated with the systemic inflammatory response but may be associated with hepatic pathology in EVD.[16]

PATIENT MANAGEMENT

Supportive care remains the mainstay of treatment for patients infected with EVD, including oral and intravenous hydration, nursing care, pain management, and electrolyte repletion. Passive immunization with serum from survivors has been attempted, particularly in recent cases, but the efficacy remains unclear.[5,11] Measures of hemostatic competence, such as platelet count and function, prothrombin time and partial thromboplastin time, and thromboelastography, can guide management.

Table 2. Current Outbreak

Country	Cases	Deaths	Fatality Rate
Guinea	3,494	2,320	66%
Liberia	9,712	4,332	45%
Sierra Leone	12,022	8,547	71%
Nigeria	20	8	40%
Senegal	1	0	0%
Spain	1	0	0%
United States	4	1	25%
Mali	8	6	75%
United Kingdom	1	0	0%