Available online at www.sciencedirect.com
ScienceDirect
Virology 356 (2006) 45–49
VIROLOGY
www.elsevier.com/locate/yviro

Characterization of shock in a hamster model of hantavirus infection

Matthew J. Campen [a], Mary Louise Milazzo [b], Charles F. Fulhorst [b], Chrys J. Obot Akata [a], Frederick Koster [a,*]

[a] Pathophysiology Division, Lovelace Respiratory Research Institute, 2425 Ridgecrest Dr. SE, Albuquerque, NM 87108, USA
[b] Department of Pathology, University of Texas Medical Branch, 301 University Blvd., Galveston, TX 77555-0609, USA

Received 22 March 2006; returned to author for revision 27 April 2006; accepted 27 July 2006
Available online 6 September 2006

Abstract

Human hantavirus cardiopulmonary syndrome (HCPS) due to Andes, sin nombre and other hantaviruses is characterized by severe pulmonary capillary leak and cardiogenic shock. Hamsters, the only animal manifesting HCPS-like disease, were instrumented with radiotelemeters that enabled ambulatory intracarotid blood pressure recording within an animal biosafety level-4 facility. Following infection with Andes virus, blood pressure and heart rate decreased slowly in a biphasic manner during the first 7 days of infection, followed by a rapid fall in pressure and rapid increase in heart rate during the 10–20 h preceding death on day 9 or 10. The preterminal narrowing of pulse pressure was consistent with a cardiogenic impairment. Heart rate variability analysis implicated increased sympathetic nervous system activity as seen in human HCPS. The hamster model of HCPS mimics not only the pulmonary capillary leak but also the hypotension characteristic of human HCPS.

Keywords: Hantavirus; Shock; Radiotelemetry; Hamster; Andes virus

Introduction

Hantavirus cardiopulmonary syndrome (HCPS), first recognized in the United States in 1993 (Duchin et al., 1994), is frequently complicated by not only massive pulmonary edema but also shock (Koster and Hjelle, 2004). A cardiogenic component to the shock is suggested by ventricular wall motion abnormalities, as recorded on two-dimensional echocardiography; reduced ejection fractions and stroke work despite normal filling pressures; and normal or elevated systemic vascular resistance (Hallin et al., 1996). Current treatment is limited to supportive care, vasopressor and inotropic medications, and extracorporeal membrane oxygenation where available (Crowley et al., 1998). Infection of the Syrian golden hamster with the Andes virus (ANDV) (Hooper et al., 2001) and Maporal virus (Milazzo et al., 2002) causes an illness that mimics human disease with respect to severe pulmonary edema and large pleural effusions. Whether the infected hamster also manifests shock, be it of cardiogenic, hemorrhagic, or circulatory origin, is not known.

The biosafety level-4 (BSL-4) classification of ANDV when used in hamsters limits the potential techniques for assessing cardiac depression, as most methods for determining contractility and cardiac index are fairly invasive. We implanted radiotelemetry devices prior to infection to continuously acquire blood pressure and heart rate data in conscious, unrestrained animals. Beat-to-beat interval data were analyzed for heart rate variability patterns using frequency domain techniques to indirectly assess the cardiac autonomic balance throughout the course of disease. We confirmed that significant shock precedes death in the hamster model of ANDV infection.

Results and discussion

Infection and mortality

Consistent with the original model description (Hooper et al., 2001), ANDV was highly lethal and all hamsters infected with ANDV died between days 9 and 10 of infection. Overt signs of infection were not apparent until 24 to 36 h prior to death and were manifested as hunched posture, ruffled fur, mattering and crusting around the eyes, and paucity of movement. Blood pressure telemetry permitted an estimate of diurnal patterns of

* Corresponding author. Fax: +1 11 505 348 8567.
E-mail address: fkoster@lrri.org (F. Koster).

0042-6822/$ - see front matter © 2006 Elsevier Inc. All rights reserved.
doi:10.1016/j.virol.2006.07.044

activity and, while not quantitative, a decrease in activity was observed during the usual nocturnal hours beginning at least 48 h prior to death. Within 12 h of death, most hamsters demonstrated marked tachypnea. These clinical observations and the observed 100% mortality were similar to those previously reported (Hooper et al., 2001) although the earlier interval to death (days 9 and 10) might be due to infection of younger animals (10 weeks old) compared to death at days 11 to 14 in 14- to16-week-old hamsters.

Postmortem examination of the hamsters revealed a weight loss of approximately 5 g and large volumes (approximately 3 ml) of yellow to pink opaque fluid bilaterally in the pleural cavity. The heart appeared normal in size and in coloration; the pericardial cavity of one animal contained a small amount of fluid.

Blood samples collected from the hamsters at necropsy were tested for antibody (IgG) against ANDV, using an indirect fluorescent antibody test. The anti-ANDV antibody titers in all the virus-inoculated animals at necropsy were >40. Infectious hantavirus was isolated from samples of lung tissue from all the animals.

Hemodynamic measurements

Recordings of individual carotid arterial blood pressures exhibited a diurnal pattern varying with physical activity within the cage; periods of high activity often rendered inadequate signals due to artifactual noise. Averages of all of data from the recordings, minus the periods with uninterpretable signals, however, revealed clear trends for the group of 10 animals during the course of infection. During the first 3 days of infection following inoculation, blood pressure and heart rate decreased as did baseline systolic and diastolic blood pressures of 106 and 88 mm Hg, respectively, decreasing to 85 systolic and 72 diastolic within 72 h (Fig. 1A). The explanation for this decrease is not apparent and it may simply reflect accommodation to the environment, although the value is lower than expected normal values (Kato et al., 2003). During days 3 to 6 of infection the blood pressures appeared to stabilize, but following day 6, blood pressure began a second modest decrease until 10 to 20 h preceding mortality. Heart rates behaved similarly over the first 3 days and appeared to stabilize on day 3 but began a second phase of decrease from day 5 to roughly 10 h before death (Fig. 1B). Heart rates eventually fell to nearly half of the baseline values; again, this may be due, in part, to accommodation to the environment along with the decreased physical activity associated with the illness.

During the 12 h preceding death, blood pressure fell more rapidly (Fig. 2A) with systolic pressures falling below 75 mm Hg and diastolic pressures below 65 mm Hg, which is consistent with shock. Systolic pressure declined more rapidly than diastolic, resulting in a decrease in pulse pressure from roughly 9 mm Hg to 4 mm Hg. Heart rate increased during the final 12-h interval, increasing 20% before asystole (Fig. 2B). During the 1 to 2 h prior to death, agonal breathing patterns were observed in the blood pressure tracing.

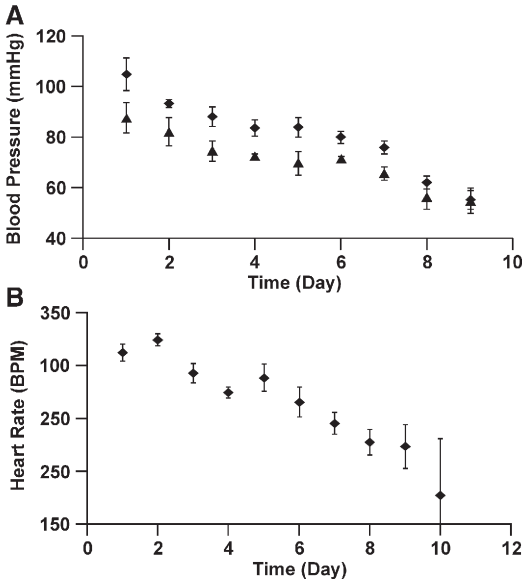

Fig. 1. Blood pressure (A) and heart rate (B) alterations over the course of ANDV-induced illness. Systolic (diamonds) and diastolic (triangles) data are shown as mean ± SE for all animals during each 24-h interval. Based on a paired ANOVA, significant decreases in blood pressure and heart rate were seen at day 4 compared to baseline, and on day 8 compared to day 4 ($p<0.01$). Variation in heart rates among the animals on the day of death (days 9 and 10) was considerable, owing to the dramatic hypotension and baroreceptor-related compensation.

The findings of decreasing pulse pressure are consistent with cardiogenic shock, but measurement of blood pressure in the absence of an independent measure of myocardial contractility and stroke work do not enable firm conclusions regarding the contribution of cardiac dysfunction to the hypotension. Other causes of shock in this disease may include (1) intravascular blood volume depletion due to capillary leak, which would be consistent with the observed weight loss; (2) mechanical interference by pulmonary edema and pleural effusions that negatively impact diastolic filling and, therefore, cardiac output; and (3) peripheral dilatation related to severe hypoxemia.

Heart rate variability

Heart rate variability (HRV) is the measurement of variations in the beat-to-beat intervals. HRV is normally somewhat chaotic but the intervals become more regular during disease. Complex mathematical analysis of interval variation yields quantitative markers of autonomic activity. These markers may reflect changes in peripheral vascular resistance that are difficult to measure in ambulatory animals. The dimensionless parameters correlating with the physiologic rhythms embedded in the intrabeat variations have been experimentally verified by a number of investigators, and summarized and standardized by a Task Force (Task Force, 1996). High frequency (HF) and root mean sum of squared deviations (RMSSD) are indices of rapid heart rate change principally affected by parasympathetic controllers. Low