

# Hemodynamic and Pulmonary Permeability Characterization of Hantavirus Cardiopulmonary Syndrome by Transpulmonary Thermodilution

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## Abstract

Hantavirus cardiopulmonary syndrome (HCPS) is characterized by capillary leak, pulmonary edema (PE) and shock that leads to death in up to 40% of patients. Treatment is supportive, including mechanical ventilation (MV) and extracorporeal membrane oxygenation (ECMO). Hemodynamic monitoring is critical to titrate therapy and to decide ECMO support. Transpulmonary thermodilution (TPTD) provides hemodynamic and PE data that has not been systematically used to understand HCPS pathophysiology. We identified 11 HCPS patients monitored with TPTD; 5 on MV, 3 on ECMO. We analyzed 133 measurements to describe the hemodynamic pattern and its association to PE. The main findings were reduced stroke volume, global ejection fraction (GEF) and preload parameters associated to increased extravascular lung water and pulmonary vascular permeability compatible with hypovolemia, myocardial dysfunction and increased permeability PE. Lung water correlated positively with heart rate (HR,  $r=0.20$ ) and negatively with mean arterial pressure ( $r=-0.27$ ) and GEF ( $r=-0.36$ ), suggesting that PE is linked to hemodynamic impairment. Pulmonary vascular permeability correlated positively with HR ( $r=0.31$ ) and negatively with cardiac index ( $r=-0.49$ ), end-diastolic volume ( $r=-0.48$ ) and GEF ( $r=-0.40$ ), suggesting that capillary leak contributes to hypovolemia and systolic dysfunction. In conclusion, TPTD data suggests that in HCPS patients, increased permeability leads to PE, hypovolemia and circulatory impairment.

**Keywords:** Hantavirus cardiopulmonary syndrome; Hantavirus pulmonary syndrome; transpulmonary thermodilution, pulmonary edema, Andes virus

## Introduction

Orthohantaviruses, members of *Hantaviridae* family, are rodent born segmented negative strand RNA viruses [1,2]. Two main categories for orthohantavirus diseases have been described: hemorrhagic fever with renal syndrome in Asia and Europe caused by “Old World”

orthohantaviruses, and on the other hand, hantavirus cardiopulmonary syndrome (HCPS), in North and South America, caused by “New World” orthohantaviruses [3].

Andes orthohantavirus (ANDV) is the Orthohantavirus endemic in Chile and Argentina and its main reservoir is the long-tailed pygmy rice rat (*Oligoryzomys longicaudatus*) [4]. Humans are infected primarily by the inhalation of aerosolized excreta from infected rodents [5,6]. Additionally, ANDV is the only orthohantavirus known to be transmissible between humans [7,10]. Indeed, in cases of ANDV infection, sexual partners and contacts who slept in the same bed during the prodromal period have been associated with ten times more risk of becoming infected when compared to other household contacts [9-10].

The incubation period of ANDV varies from 7 to 49 days [11-12], followed by cardiopulmonary phase that evolves from dry cough to respiratory failure due to capillary leak syndrome into the pulmonary interstitium, evidenced by chest radiographs showing peribronchial haze and Kerley’s B lines that subsequently progresses to alveolar flooding developing HCPS that also includes circulatory shock with myocardial depression [3,13].

Although the characteristic pathological feature of HCPS is the increased capillary permeability in lungs and depression of cardiac function, the detailed mechanism for such pathological changes remains unclear [14]. Hantaviruses primarily target endothelial cells, having  $\beta 3$  integrin receptor and protocadherin-1, for virus attachment and entry triggering non-lytic endothelial cell dysregulation [15,16]. Data from some studies, mostly carried out in cell culture models, have proposed a multifactorial mechanisms for hantavirus induced capillary leakage, for example: damage of endothelial cell barrier by up-regulated CD8 + T cell response [17]; over-expression of vascular endothelial growth factor with degradation of VE-cadherin, an important adhesion molecule that increases vascular permeability [18-20]; RhoA protein activation for Andes virus N protein, and activated RhoA who has been linked to endothelial permeability directed by thrombin, tumor necrosis factor alpha, histamine, bradykinin, and VEGF [21-23].

HCPS is one of the deadliest infectious diseases, with fatality rates of 35-40% [24-27]. Unfortunately, there are no drugs with proven efficacy for HCPS. Consequently, treatment is based on critical care support, including veno-arterial extracorporeal membrane oxygenation (VA-ECMO) [25]. The criteria to start VA-ECMO were reported for Crowley et al in 1998; cardiac index less than 2.0 L/min/m<sup>2</sup> despite maximal support and at least one of the following conditions found to be associated with a 100% mortality rate: serum lactate greater than 4.0 mmol/L (normal range 0.0–2.2), a ratio of partial pressure of arterial oxygen to fraction of inspired oxygen (PaO<sub>2</sub>:FiO<sub>2</sub>) less than 60, or cardiopulmonary deterioration, such arrhythmia or cardiac arrest [28]. These criteria highlight that the combination of hypodynamic shock (low cardiac index) and acute pulmonary edema (PE) characterize severe HCPS. It also stems from these criteria that hemodynamic monitoring is fundamental to assess the nature of circulatory impairment, to titrate resuscitative efforts and to timely decide VA-ECMO connection. Classically, hemodynamic monitoring has been performed by using the pulmonary artery catheter [25,28]. This device allows measurement of cardiac output (CO), pulmonary artery pressure, central venous pressure (CVP) and pulmonary artery occlusion pressure as indicators of right and left ventricular filling pressures, respectively [25,28]. Since early 2000 hemodynamic monitoring can be performed by single indicator transpulmonary thermodilution (TPTD). This technique allows not only to measure CO and volumetric cardiac preload, but also to assess PE at the bedside. In brief, TPTD provides two variables related to PE; extravascular lung water index (EVLWi) that quantifies it and the pulmonary vascular permeability index (PVPi), which differentiates increased permeability from hydrostatic PE [29]. EVLWi obtained from TPTD has shown close correlation with the gold standard gravimetric method [30]. Moreover, in acute respiratory distress syndrome (ARDS) patients, an EVLWi higher than 15 mL/Kg has been independently associated to mortality [31-32].

Considering that pulmonary capillary leak and circulatory dysfunction characterize HCPS, TPTD appears as a highly suitable method to assess them through the course of the disease. To date a systematic description of TPTD measurements in HCPS patients has not been performed. The aim of this study was to describe the TPTD hemodynamic pattern in patients with HCPS due to Andes orthonavirus (ANDV) admitted to a Chilean referral hospital. Additionally we explored possible associations between PE and hemodynamic variables.

## Methods

### Study design and patients

This is an observational retrospective analytical study. The cohort is part of a prospectively obtained database by the Hantavirus Program from the Instituto de Ciencias e Innovación en Medicina de la Facultad de Medicina, Clínica Alemana – Universidad del Desarrollo. For this study, only patients admitted to the adult intensive care unit (ICU) of Clínica Alemana from 2011 to 2018 were considered.

The diagnosis of HCPS was suspected on clinical grounds and confirmed in all cases by quantitative enzyme-linked immunosorbent assay (ELISA) detecting ANDV specific immunoglobulin M for or by reverse-transcription polymerase chain reaction detecting ANDV RNA. Even though ELISA and PCR cross-reactivity between orthohantaviruses is well described, substantial numbers of viruses have been sequenced in Chile and all have been ANDV [4].

Demographic, clinical, laboratory and hospital mortality data were collected using a standardized case record form, and deidentified data was entered into a dedicated database.

In Clínica Alemana, all patients with diagnosis of hantavirus diseases are admitted to the ICU considering its unpredictable and potentially fatal course. Our protocol is to monitor all patients with hantavirus diseases and respiratory and/or circulatory failure by TPTD. All the patients in this study were monitored using the PiCCO™ system (PULSION medical systems AG, Munich, Germany). TPTD was performed according to manufacturer's recommendations.

### Variables of interest

Variables obtained from TPTD can be categorized as follows:

- "Classic hemodynamic": heart rate (HR), mean systemic arterial pressure (MAP), central venous pressure (CVP), cardiac index (CI), stroke index (SI), systemic vascular resistance index (SVR<sub>i</sub>).
- Myocardial contractility: global ejection fraction (GEF), cardiac function index (CF<sub>i</sub>) and maximal change of arterial pressure per unit time (dP<sub>max</sub>).
- Volumetric preload: intrathoracic blood volume index (ITBVi) and global end diastolic volume index (GEDVi).
- Fluid responsiveness predictor: stroke volume variation (SVV).
- Pulmonary edema: extravascular lung water index (EVLWi) and pulmonary vascular permeability index (PVPi).

All these variables were available for each patient studied.

Except for SVV, which stems from systemic arterial pressure wave contour analysis, all the variables analyzed were obtained from thermodilution. All the data from all the thermodilutions performed in every patient were recorded. Values are expressed as mean±standard deviation (SD).

The institutional ethical board approved this non-interventional study with anonymized data and waived the informed consent requirement.

### Statistical analysis

An initial descriptive analysis of the patients considered was performed. All the TPTD variables obtained from all patients were descriptively analyzed. To explore possible associations between PE and hemodynamic variables, linear regressions were performed between these variables and Pearson's coefficients were obtained. To assess the behavior of hemodynamic variables according to PE severity, we dichotomized thermodilutions according to EVLWi;  $<15$  ml/Kg or  $\geq 15$  ml/kg and compared them using t-test or Mann-Whitney non-parametric test according to distributions of the sample. Normality of data distribution was assessed using the Kolmogorov-Smirnov's test. Significance was defined as p value  $<0.05$ . Statistical analysis was performed using the SPSS software, version 20 (SPSS, Chicago, IL).

### Results

Eleven patients with confirmed HCPS monitored with TPTD were identified; all required vasopressors, 5 patients required mechanical ventilation (MV), 3 required VA-ECMO support after a fairlead trial of MV and hemodynamic optimization, and 3 required non-invasive mechanical ventilation. All the patients survived and are still alive. Demographic, clinical and laboratory characteristic of these patients are shown in table 1.

Male, N (%)	7 (64)
Age, years, median [range]	29 [15-59]
SOFA score, points, median [range]	9 [4-14]
APACHE II score, points, median [range]	10 [5-30]
Invasive mechanical ventilation, N (%)	8 (73)
Inotropic drugs, N (%)	8 (73)
VA-ECMO, N (%)	3 (27)
ICU-LOS, days, median [range]	6 [4-18]
Hospital-LOS, days, median [range]	12 [4-87]

**Table 1.** Demographic, clinical and laboratory characteristics of patients with HCPS monitored with transpulmonary thermodilution (TPTD). Values are number of patients and percentage in parenthesis or median and range in square parenthesis. Sequential organ failure assessment (SOFA), acute physiology and chronic health evaluation (APACHE II), veno-arterial extracorporeal membrane oxygenation (VA-ECMO), intensive care unit (ICU), length of stay (LOS).

A total of 133 TPTD were recorded. The median [IQR] number of measurements per patient was 11 [8-15]. Descriptive analysis with normal reference values for each variable is presented in table 2. The main findings were low SI, GEF and volumetric preload parameters associated to increased EVLWi and PVPi.

Transpulmonary thermodilution variables	Median [IQR]	Reference range
<b><i>Classic hemodynamic</i></b>		
Heart rate, beats/min	99 [90-109]	60-100
Mean arterial pressure, mmHg	82 [75-89]	70-90
Central venous pressure, mmHg	8 [4-11]	6-12
Cardiac index, L/min/m <sup>2</sup>	3.1 [2.5-3.8]	3.0-5.0
Stroke index, mL/m <sup>2</sup>	34 [26-41]	40-60
Systemic vascular resistance index, dyn*s*cm <sup>-5</sup> *m <sup>2</sup>	1880 [1546-2364]	1700-2400
<b><i>Myocardial contractility</i></b>		
Global ejection fraction, %	24 [21-27]	25-35
Cardiac function index, 1/min	5.6 [5.0-6.3]	4.5-6.5
dPmax, mmHg/s	950 [762-1094]	900-1200
<b><i>Cardiac preload</i></b>		
Intrathoracic blood volume index, mL/m <sup>2</sup>	667 [553-790]	850-1000
Global end diastolic volume index, mL/m <sup>2</sup>	538 [442-635]	680-800
<b><i>Fluid responsiveness predictor</i></b>		
Stroke volume variation, %	13 [8-17]	< or = 10
<b><i>Pulmonary edema</i></b>		
Extravascular lung water index, mL/Kg	13.1 [10.2-17.3]	3.0-7.0
Pulmonary vascular permeability index, dimensionless	3.2 [2.7-4.7]	1.0-3.0

**Table 2.** Descriptive analysis of transpulmonary thermodilution (TPTD) variables. Data expressed as median and interquartile range (IQR) in square parenthesis. Reference values are given for each variable. dPmax is the maximal change of arterial pressure per second.

Correlations between PE and hemodynamic variables are summarized in table 3. Among the significant correlations between EVLWi and hemodynamic variables the most relevant positive correlations were with heart rate, CVP and volumetric preload variables; the most relevant negative correlation was between EVLWi and MAP. Among the significant correlations between PVPi and hemodynamic variables the most relevant positive correlations were with HR and SVV; the most relevant negative correlations were with CI, volumetric preload variables, GEF and CFI.

Transpulmonary thermodilution variables	EVLWi	p value	PVPi	p value
<b><i>Classic hemodynamic</i></b>				
Heart rate, beats/min	0.20	0.02	0.31	<0.01
Mean arterial pressure, mmHg	-0.27	<0.01	-0.10	0.26
Central venous pressure, mmHg	0.23	0.01	0.26	<0.01
Cardiac index, L/min/m <sup>2</sup>	0.02	0.79	-0.49	<0.01
Stroke index, mL/m <sup>2</sup>	0.06	0.51	-0.12	0.17
Systemic vascular resistance index, dyn*s*cm <sup>-5</sup> *m <sup>2</sup>	-0.18	0.04	0.38	<0.01
<b><i>Myocardial contractility</i></b>				
Global ejection fraction, %	-0.36	<0.01	-0.40	<0.01
Cardiac function index, 1/min	-0.25	<0.01	-0.20	0.02
dPmax, mmHg/s	0.12	0.18	0.16	0.08
<b><i>Cardiac preload</i></b>				
Intrathoracic blood volume index, mL/m <sup>2</sup>	0.21	0.01	-0.48	<0.01
Global end diastolic volume index, mL/m <sup>2</sup>	0.21	0.01	-0.48	<0.01
<b><i>Fluid responsiveness predictor</i></b>				
Stroke volume variation, %	0.10	0.28	0.22	0.01

**Table 3.** Pearson correlations between pulmonary edema (PE) and hemodynamic variables. PE variables are extravascular lung water index (EVLWi) and pulmonary vascular permeability index (PVPi). Hemodynamic variables are categorized as classic hemodynamic, myocardial contractility, cardiac preload and fluid responsive prediction variables. dPmax is the maximal change of arterial pressure per second.

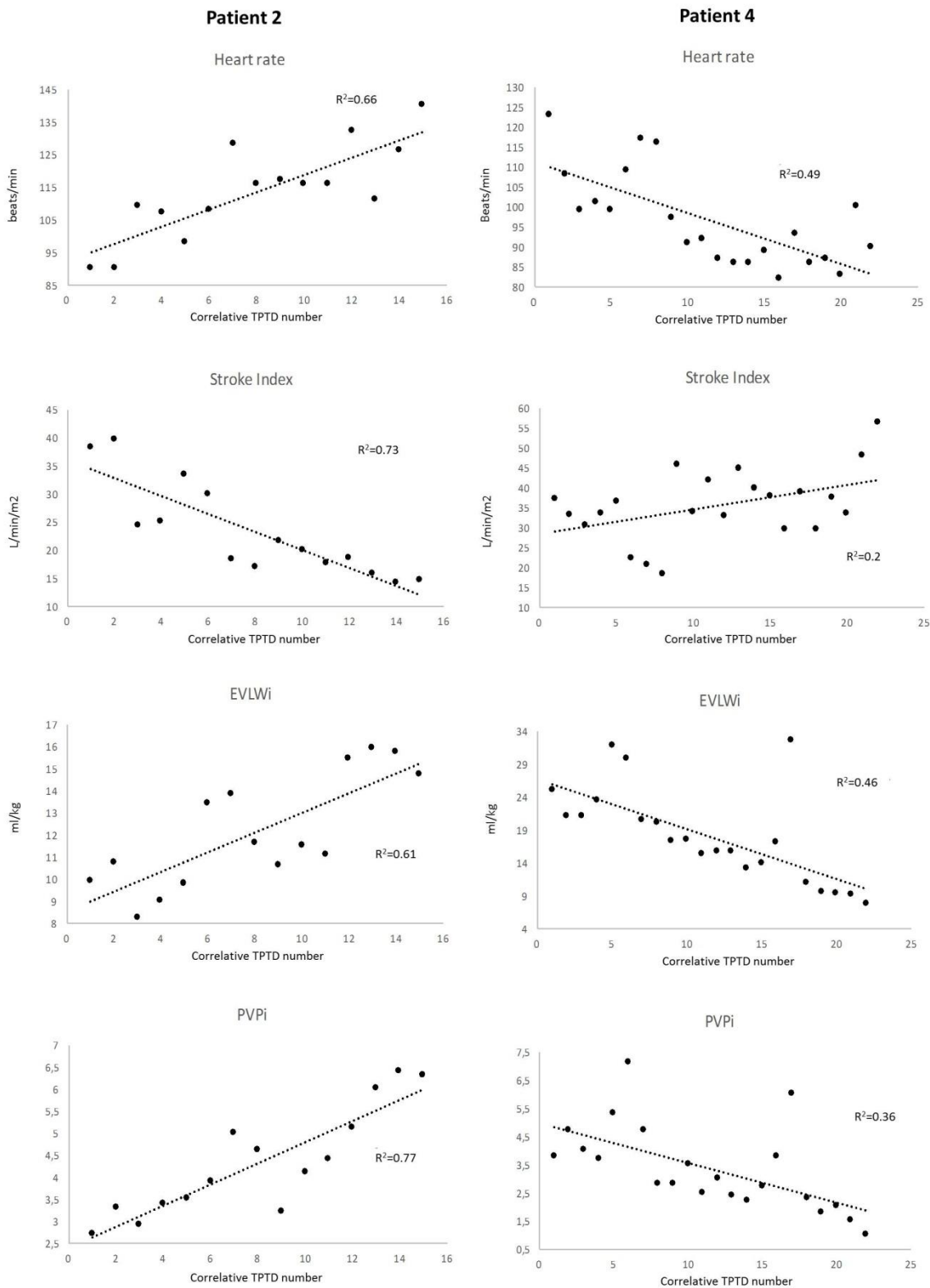
Dichotomic analysis of TPTD measurements according to EVLWi shows that when PE is severe (EVLWi  $\geq 15$  mL/kg), HR and CVP are higher while MAP, GEF and CFI are lower (table 4).

Hemodynamic variables	EVLWi <15 ml/kg	EVLWi ≥15 ml/kg	p value
<b>Classic hemodynamic</b>			
Heart rate, beats/min	96 (18)	103 (14)	0.02
Mean arterial pressure, mmHg	84 (10)	79 (9)	<0.01
Central venous pressure, mmHg	6 (4)	10 (5)	<0.01
Cardiac index, L/min/m <sup>2</sup>	3.2 (0.9)	3.1 (0.9)	0.74
Stroke index, mL/m <sup>2</sup>	34 (9)	35 (30)	0.75
Systemic vascular resistance index, dyn*s*cm <sup>-5</sup> *m <sup>2</sup>	2093 (702)	1915 (620)	0.15
<b>Myocardial contractility</b>			
Global ejection fraction, %	25 (4)	22 (5)	<0.01
Cardiac function index, 1/min	5.9 (1.1)	5.4 (0.9)	0.01
dPmax, mmHg/s	925 (223)	1007 (304)	0.12
<b>Cardiac preload</b>			
Intrathoracic blood volume index, mL/m <sup>2</sup>	680 (172)	735 (222)	0.12
Global end diastolic volume index, mL/m <sup>2</sup>	546 (138)	588 (177)	0.14
<b>Fluid responsiveness predictor</b>			
Stroke volume variation, %	13 (6)	14 (7)	0.68
<b>Pulmonary edema</b>			
Extravascular lung water index, mL/Kg	11.1 (2.2)	20.0 (4.3)	<0.01
Pulmonary vascular permeability index, dimensionless	3.1 (0.9)	5.1 (1.7)	<0.01

**Table 4.** Dichotomic analysis of transpulmonary thermodilution (TPTD) measurements according to extravascular lung water index (EVLWi) with a threshold of 15 ml/Kg. dPmax is the maximal change of arterial pressure per second. Values are mean with standard deviation (SD) in parenthesis. Comparisons were made using T-test.

Additionally, we present the time course of HR, SI, EVLWi and PVPi in a representative patient that required VA-ECMO (Patient 2) and in a representative patient that did not require VA-ECMO support (Patient 4) (figure 1). It is evident that there is an opposite trend of HR, SI, EVLWi and PVPi as one patient aggravates requiring VA-ECMO support in the end, and the other one recovers and is disconnected from MV in the end.







**Figure1.** Time course of heart rate (HR), systolic index (SI), extravascular lung water index (EVLWi) and pulmonary vascular permeability index (PVPi) in a representative patient that required veno-arterial extracorporeal membrane oxygenation (VA-ECMO) (Patient 2) and in a representative patient that did not require VA-ECMO support (Patient 4).

## Discussion

To the best of our knowledge, this is the first study that systematically describes the hemodynamic pattern, quantifies pulmonary edema and lung permeability using transpulmonary thermodilution in a cohort of patients with HCPS requiring vasopressors. Only one previous case report of suggests the usefulness of TPTD in HCPS [34]. The main findings of our study were a reduced SV compounded by low volumetric preload parameters (ITBVi and GEDVi) and a depressed myocardial contractility variable (GEF) associated to PE (increased EVLWi) with increased permeability (high PVPi). This profile is compatible with a combination of hypovolemia, systolic dysfunction and increased permeability PE. Lung water content was correlated to tachycardia, arterial hypotension and systolic dysfunction (GEF), suggesting that PE is linked to hemodynamic impairment. Pulmonary permeability was even better correlated to low volumetric preload (ITBVi and GEDVi), systolic dysfunction (GEF and CFI), hypodynamic state (CI) and tachycardia, suggesting that pulmonary capillary leak contributes to hypovolemia and systolic dysfunction. Along these lines, individual measurements with high EVLWi ( $\geq 15$  ml/Kg) were also associated to arterial hypotension and reduced systolic performance (GEF and CFI).

Our findings perfectly agree with those of the only previous systematic description of HCPS hemodynamics and lung permeability assessment by Hallin et al. in 1996, though through quite different techniques. Using the pulmonary artery catheter, chest X rays and the ratio of tracheal fluid to plasma protein and albumin concentration, they documented PE with low pulmonary artery occlusion pressure and high PE fluid to plasma protein concentration ratio in the context of circulatory shock with hypovolemia at presentation in patients with HCPS due to *Sin Nombre* virus [33]. Once fluid resuscitated, SI remained low suggesting that myocardial depression was also present in these patients [33]. We were able to quantify this PE and document the same high pulmonary permeability with TPTD in our patients. We also observed hypovolemia through volumetric preload assessment and a dynamic predictor of fluid responsiveness. Interestingly we both observed that stroke index was a better indicator of circulatory stress than CI due to compensatory tachycardia. We also observed a trait of myocardial depression mainly through the GEF, an index that relates stroke index to volumetric preload, but we were not able to document low stroke with high volumetric preload due to our restrictive approach to fluid resuscitation.

A novel observation of our report is the association of PE and increased permeability to circulatory failure with elements of both hypovolemia and myocardial depression. The association of capillary leak and hypovolemia is self-explanatory, though in contrast to “old world” orthohantaviruses, in “new world” orthohantaviruses the leak is most prominent in the lung vasculature. The association of capillary leak and myocardial depression is more intriguing. Myocardial edema is a relatively newly recognized entity and it has been shown that heart function can be significantly compromised with only small increase in the interstitial fluid [35]. One histopathologic study showed that patients who died from HCPS had more interstitial myocardial edema than other critically ill patients who died [36]. Putting together these scattered data one could speculate that capillary leak could also affect the myocardium in HCPS patients, leading to transient systolic dysfunction.

On an individual patient basis it is interesting to see that stroke index behaves as the mirror image of pulmonary permeability, lung edema and compensatory tachycardia along the course of the disease such. The course of such derangements seem also anticipate the severity of the disease and could eventually provide additional criteria for timely VA-ECMO support.

The weaknesses of our study are its retrospective nature, the small number of patients and the high variability in the number of measurements between patients. Its strengths are the large number of measurements collected for analysis and the inclusion of patients with different severities in terms of supportive therapy requirements.

In conclusion, transpulmonary thermodilution provides a bedside characterization of the hemodynamic profile in HCPS consistent with the pathophysiology of the disease and older descriptions using different diagnostic tools. Increased permeability pulmonary edema may be pathophysiologically linked to hypovolemia and eventually to myocardial depression. More studies are needed to determine if specific transpulmonary thermodilution patterns can be useful to anticipate the need for VA-ECMO support.

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