Journal of Intensive Care Medicine
2023, Vol. 38(8) 717-726

DOI: 10.1177/08850666231160664
journals.sagepub.com/home/jic

Adjunctive Hydrocortisone Improves Hemodynamics in Critically Ill Patients with Septic Shock: An Observational Study Using Transpulmonary Thermodilution

Leonie Jochheim, MD[1], David Jochheim, MD[2], Livia Habenicht, MD[3], Alexander Herner, MD[3], Jörg Ulrich, MD[3], Johannes Wiessner, MD[3], Markus Heilmaier, MD[3], Sebastian Rasch, MD[3], R.M. Schmid, MD[3], T. Lahmer, MD[3], and Ulrich Mayr, MD[3]

Abstract

Introduction: Septic shock is associated with high mortality and hemodynamic impairment. The use of corticoids is a common therapeutic tool in critically ill patients. However, data on the mechanisms and prognostic ability of hemodynamic improvement by adjunctive steroids are rare. This study primarily aimed to evaluate short-term effects of hydrocortisone therapy on catecholamine requirement and hemodynamics derived from transpulmonary thermodilution (TPTD) in 30 critically ill patients with septic shock and a 28 days mortality rate of 50%. **Methods:** Hydrocortisone was administered with an intravenous bolus of 200 mg, followed by a continuous infusion of 200 mg per 24 h. Hemodynamic assessment was performed immediately before as well as 2, 8, 16, and 24 h after the initiation of corticoids. For primary endpoint analysis, we evaluated the impact of hydrocortisone on vasopressor dependency index (VDI) and cardiac power index (CPI). **Results:** Adjunctive hydrocortisone induced significant decreases of VDI from 0.41 (0.29-0.49) $mmHg^{-1}$ at baseline to 0.35 (0.25-0.46) after 2 h ($P < .001$), 0.24 (0.12-0.35) after 8 h ($P < .001$), 0.18 (0.09-0.24) after 16 h ($P < .001$) and 0.11 (0.06-0.20) $mmHg^{-1}$ after 24 h ($P < .001$). In parallel, we found an improvement in CPI from 0.63 (0.50-0.83) W/m^2 at baseline to 0.68 (0.54-0.85) after 2 h ($P = .208$), 0.71 (0.60-0.90) after 8 h ($P = .033$), 0.82 (0.6-0.98) after 16 h ($P = .004$) and 0.90 (0.67-1.07) W/m^2 after 24 h ($P < .001$). Our analyses revealed a significant reduction in noradrenaline requirement in parallel with a moderate increase in mean arterial pressure, systemic vascular resistance index, and cardiac index. As a secondary endpoint, our results showed a significant decrease in lung water parameters. Moreover, changes in CPI (ΔCPI) and VDI (ΔVDI) after 24 h of hydrocortisone therapy revealed accurate prognostic ability to predict 28 days mortality (AUC = 0.802 vs 0.769). **Conclusion:** Adjunctive hydrocortisone leads to a rapid decrease in catecholamine requirement and a substantial circulatory improvement in critically ill patients with septic shock.

Keywords

septic shock, hydrocortisone, transpulmonary thermodilution, intensive care unit, vasopressor dependency index, cardiac power index

Introduction

Sepsis is the primary cause of death from infection with substantial implications for health care systems worldwide.[1–4] According to the Third International Consensus Definitions for Sepsis and Septic shock, sepsis is a life-threatening syndrome caused by a disturbed host response to infection.[5] Multifaceted inflammatory as well as non-immunologic pathways can lead to septic shock with circulatory impairment and progressive multi-organ failure (MOF).[5–9] Consequently, optimization of treatment is of major importance to improve outcome. The hypothalamic-pituitary-adrenal axis plays a crucial role in adequate host response to infection and critical illness-related corticosteroid insufficiency (CIRCI) is highly frequent in intensive care units (ICU).[10] Although steroids such as hydrocortisone (HC) are widely used as adjunctive immune-modulatory therapy, the effect of HC in critically ill patients with septic shock is still vague.[11–13]

[1]Klinik für Gastroenterologie und Hepatologie, Uniklinikum Essen, Essen, Germany
[2]Medizinisches Versorgungszentrum MVZ Jochheim Medizin, Hattingen, Germany
[3]Medizinische Klinik und Poliklinik II, Klinikum rechts der Isar, Technische Universität München, München, Germany

Corresponding Author:
Ulrich Mayr, Medizinische Klinik und Poliklinik II, Klinikum rechts der Isar, Technische Universität München, Ismaninger Straße 22, München D-81675, Germany.
Email: ulrich.mayr@mri.tum.de

Over the last decade, large randomized trials showed controversial results on the use of HC in the setting of septic shock.[12,14,15] Nevertheless, a recent meta-analysis demonstrated reduced ICU length of stay and improved outcomes after administration of HC in severe septic shock.[15] However, it remains uncertain whether steroid-related positive effects are attributable to earlier hemodynamic recovery and consecutively faster withdrawal of vasopressor therapy. Preservation of sufficient mean arterial pressure (MAP) is a key target in shock therapy,[16] but MAP is highly dependent on current catecholamine doses. For this reason, former studies evaluated the prognostic value of vasopressor dependency index (VDI) based on the relationship between vasopressor requirement and response of MAP.[17,18]

Accurate hemodynamic assessment in ICU-setting is an attractive goal in clinical trials.[19,20] Transpulmonary thermodilution (TPTD) is an invasive but practical device combining measurement of systolic function via pulse contour analysis with volumetric assessment of preload and lung water parameters.[21,22] Additionally, TPTD allows calculation of cardiac power index (CPI) in watts based on the product of left ventricular output and MAP. Previous studies demonstrated a strong predictivity of CPI for mortality in cardiogenic shock.[23,24] However, experiences on the prognostic role of CPI derived from TPTD in sepsis are rare, although myocardial dysfunction is a common sepsis-related problem.[25]

Moreover, sufficient data on the effect of HC on circulatory performance assessed by TPTD in patients with septic shock are still lacking. Therefore, the purpose of this study was to elucidate the potential short-terms effects after intravenous HC-application in ICU-patients with septic shock and monitoring via TPTD. As primary endpoint variables, we investigated the course of VDI and CPI after 24 h of corticoid therapy.

Methods

Study Design and Ethical Aspects

This is a single-center observational study including patients with septic shock treated in an eight-bed university hospital ICU (Klinikum rechts der Isar, Technical University, Munich, Germany). The study was approved by the institutional ethics committee (Ethikkommission der Fakultät für Medizin der Technischen Universität München, Project number 5384/21) and written informed consent was obtained from all patients or their legal representatives.

Between January 2017 and January 2020, we identified 40 critically ill patients fulfilling the predefined criteria for septic shock as explained further below. A total of 38 patients with feasibility of TPTD and HC therapy were screened, whereas TPTD was not feasible in two patients. All patients were followed up for a minimum observation time period of 28 days. Noradrenaline was the exclusively used catecholamine in all included ICU-patients. We excluded three patients who passed away during the first 24 h after initiation of HC. Another three patients were excluded due to additional catecholamine therapy with adrenaline or dobutamine and two patients were excluded due to incomplete assessment of

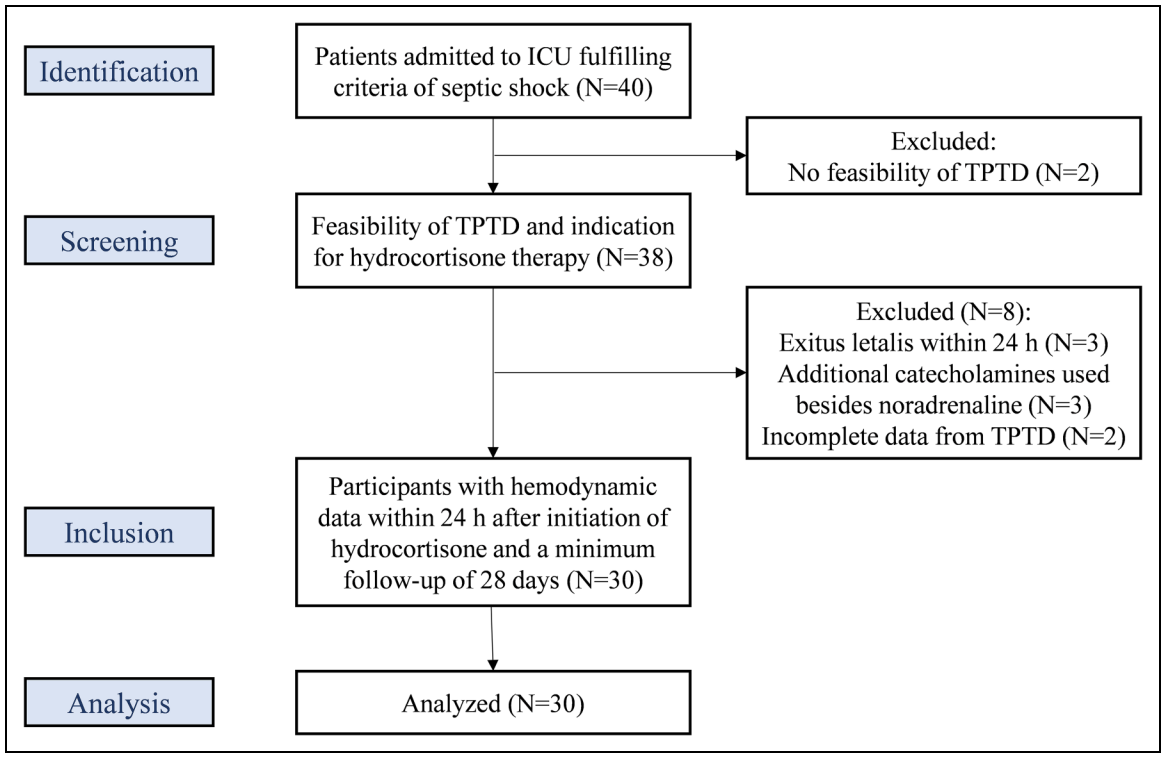

Figure 1. Flow diagram declaring subject's participation according to STROBE statement.

hemodynamic data. Finally, a total of 30 patients were analyzed in this study. A flow diagram according to the STROBE statement is illustrated in Figure 1. The screening period ended with the beginning of the COVID-19 pandemic.

Definitions of Sepsis and Septic Shock

In the present study, we used definitions following the current recommendations from the Third International Consensus Definitions for Sepsis and Septic Shock[5]: Diagnosis of sepsis was based on the evidence of organ dysfunction as a response to a clinically or microbiologically documented infection, with a sequential organ failure assessment (SOFA) score of two points or more. Identification of septic shock referred to clinical criteria of prolonged hypotension requiring vasopressor therapy (noradrenaline) to maintain a mean arterial pressure (MAP) of at least 65 mmHg and an elevated serum lactate level of 2 mmol/L or more.[16]

Hemodynamic Monitoring by Transpulmonary Thermodilution

For TPTD we used the PiCCO-2-device (Pulsion Medical Systems SE, Maquet Getinge Group) as described previously.[26] TPTD was performed irrespective of this study immediately before as well as 2, 8, 16, and 24 h after the initiation of hydrocortisone therapy by using a five-French thermistor-tipped catheter (Pulsiocath PV2015L20; Pulsion Medical Systems SE) placed in the femoral artery. After injection of a cold indicator bolus (15 mL of saline cooled down to 4°C) through a jugular central venous catheter hemodynamic curve and parameters were derived from a dedicated monitor system (PiCCO-2, Pulsion®Medical Systems, Maquet Getinge Group). Measurements were done in triplicate, averaged, and automatically indexed according to manufacturer's recommendations. Data from pulse contour analysis including cardiac power index (CPI) [W/m²]) ($=0.0022 \times$ cardiac index $\times$ MAP) and vasopressor dosage were recorded in parallel with TPTD.

As described previously, vasopressor dependency index (VDI) was derived from the ratio of catecholamines inotropic score and the current arterial pressure (noradrenaline dose as expressed in μg/kg/min $\times$ 100/MAP).[17,18]

Ventilator Setting and Respiratory Function

For mechanical ventilation, we used the EVITA XL device (Dräger, Lübeck, Germany) offering a continuous assessment of fraction of inspired oxygen (F_iO_2), positive end-expiratory pressure (PEEP), and mean airway pressure (P_{mean}). Parameter setting followed current ARDSNet recommendations.[27] Arterial partial pressure of oxygen (p_aO_2) was measured via fully-automatic blood gas analysis (Rapid Point 400, Siemens Healthcare Diagnostic GmbH, Eschborn, Germany). Corresponding variables served for calculation of Horowitz-index (p_aO_2/F_iO_2) and Oxygenation Index ($OI = F_iO_2 \times$ mean airway pressure $\times 100/p_aO_2$).[28]

Hydrocortisone Therapy

HC was administered following current recommendations irrespective of this study. Indication for adjunctive corticosteroids was based on international guidelines for the management of septic shock: According to a statement on additional therapies by the Surviving Sepsis Campaign (SSC), the use of corticosteroids is suggested in case of ongoing requirement for vasopressor therapy[29]: HC should be considered if hemodynamic stability is not achievable by adequate "initial resuscitation" with at least 30 mL/kg of crystalloids.[29] Analogously, the institutional protocol in our ICU provides initiation of HC in septic shock with circulatory impairment unresponsive to adequate volume resuscitation and demanding steady catecholamine therapy to achieve a target MAP of $\geq$ 65 mmHg.[12] After baseline TPTD-assessment, HC was administered with an intravenous bolus of 200 mg, followed by a continuous infusion of a total of 200 mg per 24 h. HC was continued for further 5-7 days – or until ICU-discharge or death.

Laboratory and Microbiological Analyses

We focused on the evaluation of parameters included in Acute Physiology and Chronic Health Evaluation II Score (APACHE) and Sequential Organ Failure Assessment Score (SOFA). In addition, we analyzed lactate level as well as common proinflammatory parameters C-reactive protein (CRP) and procalcitonin (PCT) 24 h after initiation of hydrocortisone in comparison to baseline. Laboratory assessment was performed by the department of clinical laboratory chemistry (Klinikum rechts der Isar, Technical University, Munich, Germany).

Routine screening for infections was done in all critically ill patients irrespective of this study. For microbiological analyses, we used conventional culture techniques performed by the local department of microbiology. We examined a minimum of two pairs of blood cultures to identify bacteremia. In addition, we tested urine culture, broncho-alveolar lavage (BAL), and ascitic specimens where it was feasible.

Data Collection and Endpoints

Baseline characteristics were recorded on the day of HC initiation. Assessment of TPTD, hemodynamic parameters, and vasopressor requirement was done immediately before as well as 2, 8, 16, and 24 h after the start of HC.

For primary endpoint analysis, we examined the effects of corticoids on VDI as well as CPI within 24 h after first application of HC. Secondary endpoints were measurement of changes in parameters of cardiac output, cardiac preload, systemic vascular resistance index (SVRI), noradrenaline requirement, lung water parameters, respiratory function, levels of serum lactate, and inflammatory parameters. Furthermore, we evaluated the prognostic ability of changes in CPI and VDI (ΔCPI and ΔVDI) to predict 28 days mortality.

Statistical Analyses

All statistical analyses were performed using GraphPad Prism 8.0 (GraphPad Software, La Jolla, CA, USA). We used a P-value <

.05 to determine statistical significance and expressed continuous variables as median with interquartile range (IQR) and categorical variables as percentages. Comparison between different groups of continuous data was achieved by using two-tailed Wilcoxon rank sum test for paired samples. Receiver-operating-characteristic curves (ROC) were assessed to analyze the prognostic ability of ΔCPI, ΔVDI, and other parameters to predict 28 days of mortality via area under curve (AUC). To identify the appropriate cut-offs we calculated highest combined sensitivity and specificity using Youden's index.

Results

Patient's Characteristics

A total of 30 patients were included, consisting of 10 female and 20 male patients. Patient's baseline characteristics and clinical scores are presented in Table 1.

All patients fulfilled the most recent criteria of septic shock. Systemic therapy with HC was initiated 4 (3–8) days after admission to ICU. Sepsis was predominantly of pulmonary (40%), intra-abdominal (20%), or urinary origin (17%). Most frequent microbial detections as well as most commonly used anti-infectives are listed in Supplementary File 1. Specimens of six patients revealed multi-drug resistant (MDR) bacteria with Vancomycin-resistant Enterococcus (VRE) faecium ($N=2$), Klebsiella pneumoniae ($N=2$), and Pseudomonas aeruginosa ($N=1$) resistant to aminopenicillins-third-generation-cephalosporins-fluoroquinolons-carbapenems and Methicillin-resistant Staphylococcus aureus (MRSA, $N=1$).

Table 1. Baseline Characteristics.

Patients' baseline characteristics	
Female sex, *N*/total (%)	10/30 (33%)
Age, years	66 (56-75)
Body weight, kg	81 (72-92)
Body height, cm	176 (170-180)
Body mass index, kg/m^2	26.5 (23.1-28.4)
APACHE II	26 (22-30)
SOFA	13 (12-15)
MAP, mmHg	72 (67-83)
Noradrenaline dose, μg/kg/min	0.29 (0.23-0.41)
Heart rate, min^{-1}	109 (90-123)
Atrial fibrillation, *N*/total (%)	4/30 (13%)
Lactate, mmol/L	2.8 (2.4-3.5)
CRP, mg/dL	15.3 (6.5-24.3)
PCT, ng/dL	8.6 (2.2-23.5)
ICU-admission diagnoses, *N*/total (%)	ARDS/pneumonia 11/30 (37%)
	Sepsis 9/30 (30%)
	Intestinal perforation 4/30 (13%)
	Pancreatitis 3/30 (10%)
	Acute on chronic liver failure 3/30 (10%)
Mode of ventilation, *N*/total (%)	Spontaneous breathing 2/30 (7%)
	Pressure-supported 13/30 (43%)
	Pressure-controlled 15/30 (50%)
PEEP-level, cmH_2O	8 (7-12) (N = 28)
F_iO_2, %	50 (39-66)
28 days mortality, N/total (%)	15/30 (50%)
Clinical cause of death, N/total (%)	Respiratory insufficiency 7/15 (47%)
	Cardiocirculatory failure 5/15 (33%)
	Acute on chronic liver failure 2/15 (13%)
	Gastrointestinal bleeding 1/15 (7%)

Abbreviations: APACHE, Acute physiology and chronic health evaluation; SOFA, Sequential organ failure assessment; MAP, Mean arterial pressure; CRP, C-reactive protein; PCT, Procalcitonin; ICU, Intensive care unit; ARDS, Acute respiratory distress syndrome; PEEP, Positive end-expiratory pressure; F_iO_2, Fraction of inspired oxygen.

Primary Outcome Analyses

Regarding the primary endpoint, we found a significant improvement in VDI from 0.41 (0.29-0.49) mmHg^{-1} at baseline to 0.35 (0.25-0.46) after 2 h ($P<.001$), 0.24 (0.12-0.35) after 8 h ($P<.001$), 0.18 (0.09-0.24) after 16 h ($P<.001$) and finally 0.11 (0.06-0.20) mmHg^{-1} ($P<.001$, Figure 2A). In addition, there was a stepwise improvement in CPI from 0.63 (0.50-0.83) W/m^2 at baseline to 0.68 (0.54-0.85) after 2 h ($P=.208$), 0.71 (0.60-0.90) after 8 h ($P=.033$), 0.82 (0.6-0.98) after 16 h ($P=.004$) and 0.90 (0.67-1.07) W/m^2 after 24 h ($P<.001$, Figure 2B).

Hemodynamic Parameters

As described in Table 2, circulatory monitoring combined with TPTD revealed somewhat divergent effects of HC therapy on single hemodynamic parameters.

Our results showed a rapid decrease in noradrenaline dosage (NOR) from 0.29 (0.23-0.41) μg/kg/min at baseline to 0.24 (0.18-0.34) after 2 h ($P<.001$), 0.18 (0.10-0.24) after 8 h ($P<.001$), 0.14 (0.07-0.18) after 16 h ($P<.001$) and 0.08 (0.04-0.15) μg/kg/min after 24 h ($P<.001$, Figure 3A). In comparison, we found only marginal changes in MAP from initially 72 (67-83) mmHg to 74 (68-80) after 2 h ($P=.931$), 77 (72-84) after 8 h ($P=.162$), 80 (72-82) after 16 h ($P=.130$) and finally statistically significant 79 (75-83) mmHg after 24 h ($P=.042$, Figure 3B). Moreover, our analyses after 24 h revealed a modest but statistically significant increase in systemic vascular resistance index (SVRI) ($P=.006$) and cardiac index CI ($P=.018$). Pulse contour analysis showed a slight decrease in stroke volume variation (SVV) after 24 h ($P=.028$).

By contrast, TPTD showed no statistically significant changes in stroke volume index (SVI) or global ejection fraction (GEF). Similarly, we found no relevant changes over time in parameters of circulatory preload global end-diastolic volume index (GEDVI) or central venous pressure (CVP).

Laboratory Parameters

Based on an overall interval of 24 h after initiation of HC, our laboratory analyses revealed a statistically significant decrease

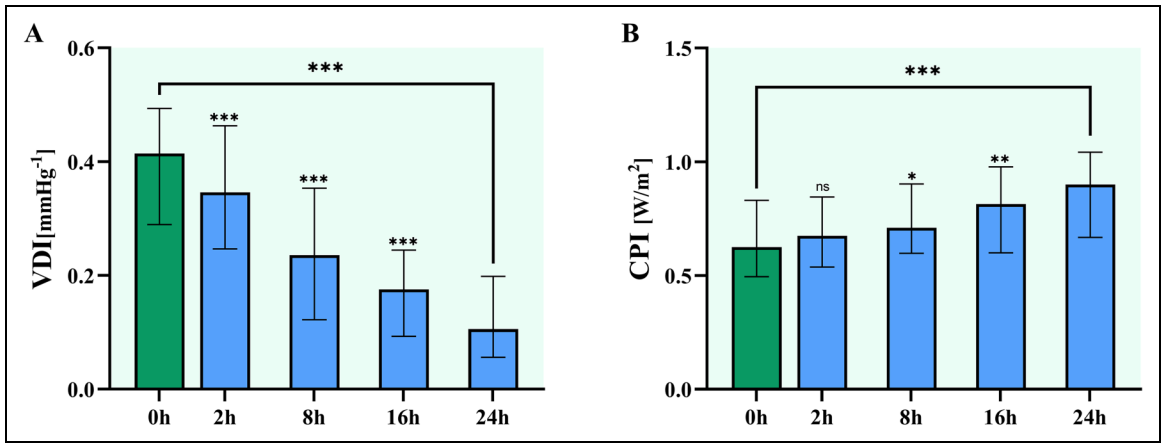

Figure 2. Hemodynamic parameters of primary outcome analysis at baseline as well as 2, 8, 16, and 24 h after initiation of hydrocortisone (HC) therapy: [A] Vasopressor dependency index (VDI) [B] Cardiac power index (CPI) assessed by TPTD.

Table 2. Secondary Hemodynamic Parameters Assessed by TPTD at Baseline as Well as 24 h After Initiation of HC Therapy.

Secondary hemodynamic parameters assessed by TPTD			
	At baseline Median (IQR)	24 h after initiation of HC Median (IQR)	*P*-value
Noradrenaline, μg/kg/min	0.29 (0.23-0.41)	0.08 (0.04-0.15)	<.001
MAP, mmHg	72 (67-83)	79 (75-83)	.042
SVRI, dyn × s × cm^{-5} × m^{-2}	1179 (844-1389)	1233 (926-1474)	.006
CI, L/min/m^2	4.3 (3.1-5.4)	4.7 (3.9-5.4)	.018
SVV, %	12 (9-19)	9 (7-16)	.028
SVI, mL/m^2	41 (31-53)	45 (39-50)	.199
GEF, %	23 (17-26)	25 (20-27)	.091
GEDVI, mL/m^2	850 (710-922)	835 (763-987)	.169
CVP, mmHg	18 (14-20)	19 (14-23)	.330

Abbreviations: TPTD, Transpulmonary thermodilution; IQR, Interquartile range; CPI, Cardiac power index; SVRI, Systemic vascular resistance index; SVV, Stroke volume variation; MAP, Mean arterial pressure; CI, Cardiac index; SVI, Stroke volume index; GEF, Global ejection fraction; GEDVI, Global end-diastolic volume index; CVP, Central venous pressure.

in lactate ($P = .001$) and PCT ($P < .001$). By contrast, we found no significant change in CRP (Table 3).

Lung Water and Respiratory Function

Hemodynamic monitoring via TPTD revealed a significant reduction of extravascular lung water index (EVLWI) in parallel with a decrease in pulmonary vascular permeability index (PVPI).

As illustrated in Table 4, this decrease in lung water parameters was combined with a distinct improvement in respiratory function regarding p_aO_2/F_iO_2 and oxygenation index (OI).

Additional analyses of lung water parameters at time periods of 48 h as well as 72 h indicated that the favorable effects on EVLWI and PVPI were existing for at least 72 h after initiation of steroid therapy: In comparison to baseline values, EVLWI dropped from 12 (9-15) to 10 (8-12) after 24 h ($P < .001$), 10 (8-13) after 48 h ($P < .001$) and finally 9 (8-13) mL/kg at a time period of 72 h after initiation of hydrocortisone ($P < .001$). Analogously, PVPI decreased from 1.7 (1.4-2.6) at baseline to 1.5 (1.3-2.0) after 24 h ($P = .001$), 1.6 (1.3-1.9) after 48 h ($P = .037$) and finally 1.5 (1.2-2.0) 72 h after initiation of steroids ($P = .015$).

ROC-Curves and Mortality Risk

We used ROC-curves to evaluate whether the improvements in hemodynamic parameters derived from primary outcome analyses could sufficiently predict 28 days mortality risk.

Regarding the differences in VDI and CPI after 24 h of HC therapy compared to baseline, we found a median decrease for ΔVDI of 0.30 (0.20-0.37) mmHg^{-1} as well as a median increase for ΔCPI of 0.13 (0.10-0.35) W/m^2. According to ROC-analyses, ΔCPI had a moderate prognostic advantage in predicting 28 days mortality (AUC = 0.802, $P = .005$) compared to ΔVDI (AUC = 0.769, $P = .012$). Detailed data are presented in Supplementary File 2.

In comparison, the median difference of noradrenaline dosage (ΔNOR) as a single parameter performed worse in predicting outcome: For ΔNOR we found a decrease in 0.20 (0.16-0.28) μg/kg/min and according to ROC-curves an AUC of 0.647 ($P = .171$). Concerning the drop in lactate level, our results showed a median reduction for Δlactate of 0.7 (0.1-1.3) mmol/L and an AUC of 0.711 ($P = .049$). As illustrated in Figure 4A, the prognostic accuracy of Δlactate and ΔNOR for 28 days mortality was inferior compared to ΔCPI and ΔVDI.

Analogously, we compared the discriminative ability of ΔCPI and ΔVDI for 28 days mortality to baseline values of common scoring systems in critically ill patients (Figure 4B): ΔCPI and ΔVDI showed a distinct prognostic advantage in

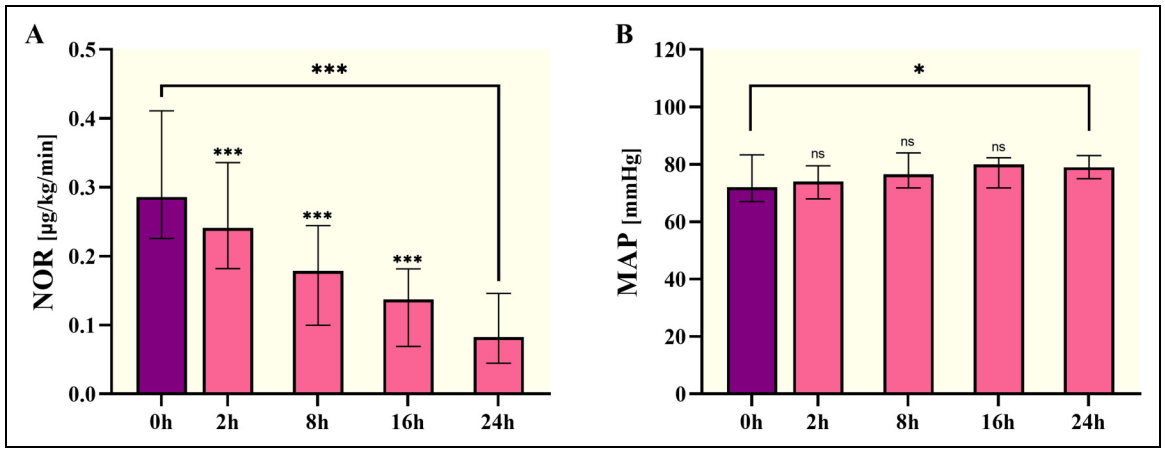

Figure 3. Secondary hemodynamic parameters at baseline as well as 2 h, 8 h, 16 h and 24 h after initiation of hydrocortisone (HC) therapy: [A] Noradrenalin dosage (NOR) [B] Mean arterial pressure (MAP).

Table 3. Laboratory Parameters at Baseline as Well as 24 h After Initiation of HC Therapy.

Laboratory parameters at baseline and after 24 h of HC therapy			
	At baseline Median (IQR)	24 h after initiation of HC Median (IQR)	*P*-value
Lactate, mmol/L	2.8 (2.4-3.5)	2.2 (1.6-3.0)	.002
CRP, mg/dL	15.3 (6.5-24.3)	15.9 (5.1-24.1)	.414
PCT, ng/dL	8.6 (2.2-23.5)	7.4 (1.4-17.7)	<.001

Abbreviations: IQR, Interquartile range; CRP, C-reactive protein; PCT, Procalcitonin.

Table 4. Lung Water Parameters and Respiratory Function at Baseline as Well as 24 h After Initiation of HC Therapy.

Lung water indices and respiratory function at baseline and after 24 h of HC therapy			
	At baseline Median (IQR)	24 h after initiation of HC Median (IQR)	*P*-value
EVLWI, mL/kg	12 (9-15)	10 (8-12)	<.001
PVPI	1.7 (1.4-2.6)	1.5 (1.3-2.0)	.001
p_aO_2/F_iO_2, mmHg	175 (132-237)	222 (145-272)	<.001
OI, cmH_2O/mmHg	8.7 (4.7-12.0)	6.4 (3.9-11.1)	<.001

Abbreviations: IQR, Interquartile range; EVLWI, Extravascular lung water index; PVPI, Pulmonary vascular permeability index; OI, Oxygenation index.

comparison to baseline SOFA (AUC = 0.716, $P = .056$) as well as APACHE (AUC = 0.662, $P = .130$).

Discussion

This study illustrates a rapid hemodynamic improvement after the administration of adjunctive HC in critically ill patients with septic shock. We evaluated the beneficial circulatory effects of corticoid therapy on vasopressor requirement combined with extended hemodynamic assessment derived from transpulmonary thermodilution (TPTD).

The main finding of the present study was a stabilization of septic shock and circulation in relation to current catecholamine dosage. Hemodynamic parameters are largely dependent on the extent of exogenous vasopressor support. Therefore, for primary endpoint analyses we examined the vasopressor dependency index (VDI) defined as the ratio of noradrenaline dosage and corresponding mean arterial pressure (MAP). Furthermore, we focused on cardiac power index (CPI) as the product of ventricular output and MAP. Initiation of intravenous HC therapy provoked a substantial improvement in both VDI as well as CPI. All significant changes occurred within a short time period after initiation of HC, supporting the hypothesis that adjunctive steroid therapy is associated with hemodynamic stabilization. Treatment with corticoids induced a rapid decrease in noradrenaline requirement, but had only a moderate impact on single hemodynamic parameters MAP or cardiac index (CI).

As secondary results, the present study demonstrates a significant change in TPTD-derived lung water parameters associated with administration of HC in ICU-patients with septic shock: EVLWI and PVPI dropped significantly after 24 h of corticoid therapy compared to baseline. Moreover, we found a substantial improvement in p_aO_2/F_iO_2 and Oxygenation index (OI) in comparison to baseline.

Another interesting secondary finding of this study was the prognostic accuracy of improvements in primary endpoint variables. In this context we analyzed the discriminative ability of median changes of VDI and CPI after 24 h of corticoid administration in relation to baseline parameters: Both ΔCPI (AUC = 0.802) as well as ΔVDI (AUC = 0.769) performed better in predicting 28 days mortality than common clinical scores SOFA, APACHE or changes in serum lactate levels.

Last but not least, this study underlines the usefulness of TPTD in a very challenging population of critically ill patients: Septic shock requires rapid detection with effective treatment to

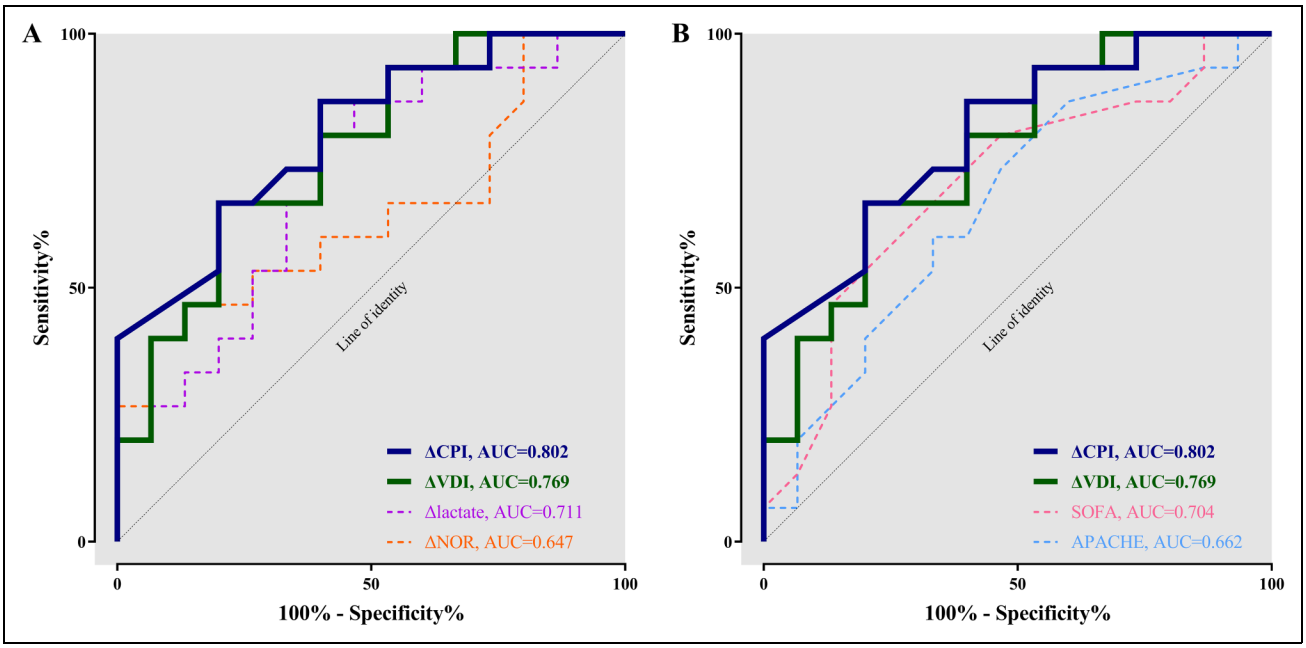

Figure 4. Receiver-operating-characteristic (ROC) curves evaluating the prognostic ability of ΔCPI and ΔVDI to predict 28 days mortality in comparison to [A] ΔNOR and Δlactate [B] baseline values of SOFA and APACHE.

prevent a fulminant clinical course.[6] In this setting, adequate monitoring of fluid management and response to catecholamines is a central aspect of treatment success. TPTD was developed to guide volume resuscitation and dosage of vasopressors or positive-inotrope drugs to maintain effective circulation.[30] However, sufficient data regarding the hemodynamic impairment in septic shock as well as the effect of corticoid application as measured by TPTD are still lacking. Therefore, a major strength of our study is that it demonstrates a rapid circulatory stabilization assessed by TPTD in ICU-patients with septic shock after adjunctive HC administration.

From a pathophysiological point of view, the rationale for the use of corticoids in septic shock relies on limiting excessive inflammatory responses while preserving innate immunity.[15] Endothelian glucocorticoid receptors might decelerate vascular permeability and increase systemic vascular resistance.[31] According to our results, circulatory improvement was associated with a moderate but still significant increase in SVRI derived from TPTD. In relation to the steadily decreasing demand on vasopressors, this increase in afterload seems to play an important role in hemodynamic stabilization by HC. By contrast, there was no relevant change of preload parameters GEDVI or CVP after 24 h of adjunctive steroid therapy. This fact supports the hypothesis of a predominantly corticoid-driven circulatory effect instead of hemodynamic improvement mainly due to liberal fluid management.

Our current findings are largely in line with the results of two previous trials investigating HC application in septic shock. In the randomized Activated Protein C and Corticosteroids for Human Septic Shock (APROCCHSS) Trial, patients receiving HC plus fludrocortisone had significantly better outcome and a lower 90 days mortality.[32] In comparison, we found an accurate prognostic ability for changes in primary hemodynamic outcome variables to predict 28 days mortality. The Adjunctive Corticosteroid Treatment in Critically Ill Patients with Septic shock (ADRENAL) Trial found no effect of HC on overall mortality, but revealed a higher incidence of shock-resolution and a shorter median time to cessation of mechanical ventilation in the HC group.[33] Our study population had a high proportion of patients with mechanical ventilation (93%), while 37% were categorized as ARDS on ICU-admission. Analyses derived from TPTD revealed a decrease in lung water after corticoid administration along with improved respiratory function. TPTD has become the gold standard in evaluating extravascular lung water and many previous studies addressed the prognostic value of EVLWI in sepsis or ARDS.[34–36] In critically ill patients with ARDS, treatment success is linked to limitation of pulmonary edema and vascular hyperpermeability.[37,38] Therefore, the improvement in TPTD-assessed parameters of lung edema in the present results could be explained by reduced vascular permeability induced by HC.

All in all, the current analysis indicates a beneficial effect of adjunctive HC administration in critically ill patients with septic shock on key parameters of hemodynamic as well as respiratory function. Despite the lack of a control group, our study is one of the first evaluating corticoid-related treatment response on circulatory variables assessed by TPTD.

Limitations

Despite its innovative results, our single center study has important limitations. First of all, this methodically complex

investigation was conducted in a small number of patients and no prior power analysis was performed. Hemodynamic assessment was restricted to a short time-interval of 24 h, outcome analyses are available only for a time period of 28 days. In addition, evaluation of corticoid effects focused on circulatory monitoring and TPTD. Neither echocardiography nor radiological or renal assessment played a role in the present study. Although inclusion criteria for diagnosis of septic shock followed current criteria, the population revealed a high variance in key parameters such as baseline levels of catecholamine requirement or MAP. There is still no general consensus on the best protocol for administration of HC: In the present study we used a comparably high cumulative dose of 400 mg within the first 24 h of treatment due to the initiation with a bolus of 200 mg. Moreover, clinical trials concerning both primary endpoint variables VDI and CPI including appropriate cut-offs in ICU-patients with septic shock are rare. The major limitation for the relevance of our results lies in the absence of a control group: Thus, there is no analysis available on differences in hemodynamic improvement or outcome between patients treated with or without HC or patients receiving HC plus fludrocortisone. Consequently, further prospective studies with an adequate control group are needed to specify the therapeutic effects of corticoids in ICU-patients with septic shock and monitoring with TPTD.

Conclusion

Primarily, the initiation of HC in patients with septic shock results in a substantial circulatory improvement in vasopressor dependency index (VDI) and cardiac power index (CPI) as monitored by TPTD. Furthermore, this study demonstrates that TPTD is feasible to monitor the hemodynamic changes and guide individualized therapy in a challenging population of ICU-patients with septic shock.

Abbreviations

TPTD	transpulmonary thermodilution
VDI	vasopressor dependency index
CPI	cardiac power index
MOF	multi-organ failure
ICU	intensive care unit
HC	hydrocortisone
MAP	mean arterial pressure
SOFA	sequential organ failure assessment
ARDS	acute respiratory distress syndrome
F_iO_2	fraction of inspired oxygen
PEEP	positive end-expiratory pressure
P_{mean}	mean airway pressure
p_aO_2	arterial partial pressure of oxygen
OI	oxygenation index
SSC	Surviving Sepsis Campaign
APACHE	acute and physiology chronic health evaluation
CRP	C-reactive protein
PCT	procalcitonin
BAL	broncho-alveolar lavage
SVRI	systemic vascular resistance index
IQR	interquartile range
ROC	receiver-operating-characteristic curves
AUC	area under curve
MDR	multi-drug resistant
VRE	vancomycin-resistant enterococcus
MRSA	methicillin-resistant staphylococcus aureus
NOR	noradrenalin dosage
SVV	stroke volume variation
CI	cardiac index
SVI	stroke volume index
GEF	global ejection fraction
GEDVI	global end-diastolic volume index
CVP	central venous pressure
EVLWI	extravascular lung water index
PVPI	pulmonary vascular permeability index

Acknowledgements

This study is dedicated to Professor Wolfgang Huber who unexpectedly passed away on May eighth, 2020. We will always remember him as an expert in the fields of hemodynamic monitoring, transpulmonary thermodilution, extra-corporal assistant devices and ARDS. As head of our intensive care unit, this study was conducted under his responsibility. Wolfgang Huber collaborated with Pulsion Medical Systems SE, Feldkirchen, Germany, as member of the Medical Advisory Board.

Authors' Contributions

LJ, UM, and TL designed the study. LJ, DJ, and UM collected data, performed statistical analysis and drafted the manuscript. LH, AH, JU, JW, MH, SR, RS, and TL also collected data, participated in the analysis of the data, and helped to draft the manuscript.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

Ethics Approval and Consent to Participate

This observational study was approved by the institutional review board (Ethikkommission Technische Universität München; Fakultät für Medizin; Project number 5384/12). Informed consent was obtained by all patients or their legal representatives.

Consent for Publication

Informed consent was obtained by all patients or their legal representatives.

Availability of Data and Material

More detailed data are available upon request. To receive anonymized data readers are welcome to contact the corresponding author: Dr

Ulrich Mayr, Klinik und Poliklinik für Innere Medizin II, Klinikum rechts der Isar der Technischen Universität München, Ismaninger Strasse 22, D-81675 München, Germany. Fax: 0049-89-4140-4742. E-mail: mayr.ulrich@gmx.net

ORCID iD

Ulrich Mayr https://orcid.org/0000-0002-5235-5327

Supplemental Material

Supplemental material for this article is available online.

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