Effects of hydrocortisone on microcirculatory alterations in patients with septic shock*

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Objective: **To evaluate the effects of hydrocortisone on microcirculatory blood flow alterations in patients with septic shock.**

Design: **Prospective, open-label study.**

Setting: **A 31-bed, medico-surgical intensive care unit of a university hospital.**

Patients: **Twenty patients with septic shock.**

Interventions: **Intravenous hydrocortisone (50 mg/6 hr).**

Measurements and Main Results: **An orthogonal polarization spectral device (Cytoscan ARII, Cytometrics; Philadelphia, PA) was used to investigate the sublingual microcirculation in 20 patients who received so-called "stress doses" of hydrocortisone as part of their management for septic shock. Hemodynamic measurements and orthogonal polarization spectral images were obtained before administration of the first dose (50 mg) of hydrocortisone and 1, 2, 4, and 24 hours later. Measurements were also made before an adrenocorticotropic hormone (ACTH) test, whenever performed. Global hemodynamic variables were similar at all study time points. Microcirculatory variables improved slightly already at 1 hour after the start of hydrocortisone administration. In particular, perfused vessel density increased from 5.7 (4.8–6.4) to 7.2 (6.5–9.0)n/mm, $p < 0.01$, which was due to combined increases in small vessel density from 5.2 (4.6–6.2) to 6.0 (5.1–7.5)n/mm, $p < 0.01$, and in the proportion of perfused vessels from 82.1 (68.7–88.0) to 89.2 (83.4–92.6)%, $p < 0.01$. There were no differences in microcirculatory variables during hydrocortisone administration between ACTH test responders and nonresponders.**

Conclusions: **The administration of moderate doses of hydrocortisone in septic shock results in a modest but consistent improvement in capillary perfusion, independent of the response to the ACTH test. The mechanisms underlying this effect need to be elucidated. (Crit Care Med 2009; 37:1341–1347)**

KEY WORDS: septic shock; steroids; microcirculation; regional blood flow; orthogonal polarization spectral imaging; intensive care

Septic shock is an important cause of death in critically ill patients worldwide (1, 2). Microvascular alterations are frequent in patients with septic shock, even when global oxygen delivery seems adequate, and may play an important role in the development of organ failure (3, 4). Numerous experimental studies have reported that microvascular blood flow is altered in sepsis and common findings include a decrease in functional capillary density and heterogeneity of blood flow with perfused capillaries in close vicinity for nonperfused capillaries. Multiple factors may contribute to these findings, including alterations in red blood cell rheology and leukocyte adhesion to endothelial cells, endothelium dysfunction, and interstitial edema. The orthogonal polarization spectral imaging technique has become a useful tool to investigate the microcirculation (5), as it allows the direct visualization of the microvasculature at the bedside. With this technique, our group and others have shown that patients with severe sepsis and septic shock have a decrease in the proportion of perfused capillaries compared with healthy volunteers (3, 6, 7) and that persistent microvascular alterations are associated with the development of organ failure and death (4). The orthogonal polarization spectral technique can also be used to evaluate the effects of various interventions on the microcirculation (6, 8–10).

Moderate doses of corticosteroids have been advocated as part of the management of patients with septic shock (11, 12), even though the outcome benefit of this strategy has recently been challenged (13). This recommendation is largely based on the frequent observation of relative adrenal insufficiency in patients with septic shock (14–18) and on clinical trials showing a more rapid resolution of shock (11, 17, 19), and even a decrease in mortality rate (11), in patients receiving hydrocortisone. As hydrocortisone improves vascular tone in patients with septic shock (20), one may expect that hydrocortisone would impair microvascular blood flow. Indeed, topical glucocorticoids have vasoconstricting effects in normal skin, known as a *positive blanching test* (21). However, the response of skin perfusion may differ from other microvascular beds in patients with sepsis (22), and the effects of hydrocortisone on the microcirculation have not been well defined. In this study, we evaluated the effect of hydrocortisone administration on sublingual microcirculatory alterations in patients with septic shock.

PATIENTS AND METHODS

The study was approved by the local ethics committee and informed consent was obtained from the patients or their relatives.

The study included 20 patients in the first 12 hours of septic shock, as defined by the

***See also p. 1509.**

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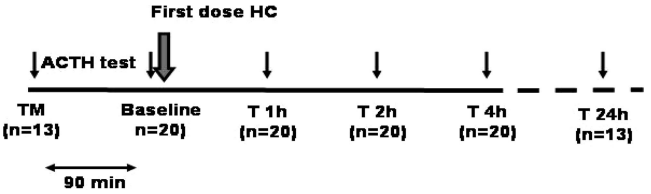

Figure 1. Timing of measurements in study protocol. *TM*, initial measurement; *HC*, hydrocortisone; *arrow*, measurement (hemodynamic and OPS).

Table 1. Baseline characteristics of patients

Characteristic	Value
Age (yrs)	69 (58–75)
Male sex, n (%)	16 (80)
Acute Physiology and Chronic Health Evaluation II score[a]	21 (19–26)
Sequential Organ Failure Assessment score[a]	11 (9–13)
Intensive care unit length of stay (days)[a]	12 (6–20)
Alive at 28 days, n (%)	13 (65)
Source of infection, n (%)	
Lung	9 (45)
Abdomen	8 (40)
Urinary tract	2 (10)
Soft tissue	1 (5)

[a]Values expressed as median (1st–3rd quartile).

International Sepsis Definition Conference (23). Exclusion criteria were pregnancy, age <18 years, liver cirrhosis, shock due to another cause than sepsis or lasting for >24 hours, advanced malignancy, or expected survival of <2 months because of the underlying disease.

According to our local guidelines, each patient was equipped with an arterial and a central venous catheter; 15 patients were also monitored with a pulmonary artery catheter (CCO pulmonary artery flotation catheter; Edwards, Irvine, CA). Treatment of septic shock was standardized, including vasopressors to maintain mean arterial pressure (MAP) >65 mm Hg in addition to repeated fluid challenges with crystalloids and artificial colloids (gelatin or hydroxyethyl starch solutions) to increase stroke volume and/or allow the doses of vasopressors to be decreased. Vasopressor therapy consisted of dopamine alone (up to 20 μg/kg/min) and/or norepinephrine. Epinephrine was not used routinely. All patients were receiving mechanical ventilation under light sedation (midazolam up to 4 mg/hr) and analgesia (morphine up to 3 mg/hr or remifentanil up to 4 μg/min). Drotecogin alfa (activated) (DAA) was given when indicated according to the European/Belgian criteria.

Intravenous hydrocortisone (50 mg/6 hr) was started, usually after completion of an adrenocorticotropic hormone (ACTH) test (250 μg, measurements of cortisol at 0, 30, 60, and 90 minutes). In patients with a normal cortisol response to an ACTH test (i.e., a cortisol increment higher than 9 μg/dL [14, 16, 18]), hydrocortisone was discontinued within 24 hours, as soon as the results of the test were available. In the other patients, hydrocortisone was administered for 7 days. Fludrocortisone was not administered.

Temperature, heart rate, arterial pressure, central venous pressure, and complete hemodynamic measurements, in patients with a pulmonary artery catheter, were obtained at baseline (and before ACTH test when it was performed), and 1, 2, 4, and 24 hours after the first dose of hydrocortisone (Fig. 1). Arterial and mixed venous blood samples were withdrawn simultaneously for measurements of blood gases, hemoglobin concentration, hemoglobin saturation, and lactate concentrations (ABL 700, Radiometer, Copenhagen, Denmark). The Acute Physiology and Chronic Health Evaluation II score (24) was obtained at study inclusion, and the Sequential Organ Failure Assessment score was calculated (25). Outcome was assessed at 28 days.

Microvideoscopic Measurements and Analysis. Measurements of the microcirculation were obtained by an investigator (D.D.B. or G.L.B.) well trained in orthogonal polarization spectral image acquisition. The Cytoscan ARII (Cytometrics; Philadelphia, PA) with a ×5 objective (providing an ×167 magnification) was used to study the sublingual microvascular network (3). The device was gently applied without pressure to the lateral side of the tongue, in an area approximately 1.5–4 cm from the tip of the tongue after gentle removal of saliva and other secretions with gauze. Five sequences of 20 seconds each from different adjacent areas were recorded using a computer and a videocard (MicroVideo; Pinnacle System, Mountain Views, CA). These sequences were stored under a random number and later analyzed semi-quantitatively by an investigator blinded to the origin of the sequences (3, 26). Three equidistant horizontal and three vertical lines were drawn. The vascular density was calculated as the number of vessels crossing these lines divided by the total length of the lines. The type of flow was defined as continuous, intermittent, or absent. The vessels were separated into large and small vessels using a cutoff value of 20 μm in diameter. Vessel perfusion (total, large, and small) was defined as the proportion of perfused vessels, calculated as the number of vessels continuously perfused during the 20-second observation period divided by the total number of vessels of the same type. Perfused vascular density (total and small) was calculated as the product of vascular density and perfused vessel density of vessels of same type. In each patient, the data from the five areas were averaged. The intra- and interobserver variability have been determined previously and are satisfactory (3). The images were analyzed by batch by the same investigator (GB), with control of one image every 10–20 images by the senior investigator (D.D.B.) to avoid any drift in measurements. Given the intrinsic variability of measurements and previous data showing delineation between survivors and nonsurvivors (4), an absolute change of 7% to 10% in the proportion of perfused small vessels can be considered as clinically significant.

Statistical Analysis. Data were analyzed using SPSS (SPSS, Chicago, IL). A Kolmogorov-Smirnov test was used to verify the normality of distribution. A Wilcoxon's rank sum test with Bonferroni correction was used for intragroup comparisons. A general linear model for repeated measurements was used to evaluate differences in variables between the ACTH test responders and nonresponders subgroups. A p value <0.05 was considered as significant.

RESULTS

The characteristics of the 20 patients are shown in Table 1. Three patients were already being treated with continuous venovenous hemofiltration at baseline. The hemodynamic characteristics from the patients at each study time are listed in Table 2. There were no significant differences in the hemodynamic variables at any time compared with baseline. Dopamine (with or without norepinephrine) was administered in 30% of patients (and norepinephrine alone in 70%). Nine patients (45%) were also treated with dobutamine from baseline. The mortality rate at 28 days was 35% (seven patients). No major therapeutic interventions, such as surgery, continuous venovenous hemofiltration, or blood transfusion, were instituted during the observational period. All patients were sedated and receiving mechanical ventilation. Five patients received DAA during the study, but four of them had already being receiving DAA for >4 hours before hydrocortisone administration. DAA was initiated in one patient after baseline measurements; exclusion of this patient did not alter the results and accordingly the results of the entire cohort are presented.

There was no significant change in global hemodynamics over time (Table

Table 2. Hemodynamic data

	Baseline	Hydrocortisone 1 hr[a]	Hydrocortisone 2 hr[a]	Hydrocortisone 4 hr[a]	Hydrocortisone 24 hr[a,b]
Mean arterial pressure (mm Hg)	72 (66–78)	73 (68–79)	74 (68–82)	75 (69–83)	75 (70–79)
Pulmonary artery occlusion pressure (mm Hg)[c]	18 (14–21)	18 (15–21)	18 (14–22)	17 (15–20)	16 (15–19)
Central venous pressure (mm Hg)	14 (11–18)	15 (11–20)	15 (11–21)	14 (12–19)	15 (14–20)
CO (L/min)[c]	5.8 (5.0–6.6)	6.0 (5.1–7.7)	5.6 (5.1–7.3)	6.2 (5.2–7.6)	6.0 (4.7–6.3)
Lactate (mEq/L)	2.1 (1.4–3.5)	2.2 (1.4–3.7)	2.2 (1.6–4.2)	2.2 (1.6–3.7)	1.9 (1.4–3.3)
Norepinephrine, μg/kg.min [n]	0.2 (0.12–0.79) [18]	0.2 (0.12–0.84) [17]	0.2 (0.14–0.79) [17]	0.2 (0.16–0.61) [18]	0.17 (0.12–0.52) [10]
Dopamine, μg/kg.min [n]	15 (7–20) [6]	15 (7–20) [6]	15 (7–20) [6]	13 (6–20) [6]	15 (7–20) [3]
Dobutamine, μg/kg.min [n]	11 (5–16) [9]	8 (5–14) [9]	6 (5–16) [9]	6 (4–16) [9]	12 (4–18) [7]
pH	7.35 (7.26–7.36)	7.35 (7.21–7.37)	7.36 (7.21–7.39)	7.37 (7.20–7.39)	7.32 (7.29–7.42)
SvO_2, %	69 (60–73)	69 (63–73)	65 (62–73)	68 (61–71)	67 (59–70)
FIO_2, %	60 (45–80)	60 (45–80)	55 (45–60)	60 (50–70)	50 (40–60)
PaO_2, mm Hg	83 (71–125)	84 (77–105)	79 (73–97)	80 (72–107)	79 (66–73)
$PaCO_2$ (mm Hg)	38 (33–43)	37 (31–42)	39 (32–43)	37 (34–41)	35 (31–41)
Positive end-expiratory pressure (cm H_2O)	9 (5–14)	8 (5–14)	9 (5–12)	9 (5–12)	10 (5–11)

[a]All p values = ns, compared with baseline; [b]n = 13 for the study time 24 hrs; [c]n = 15. All values expressed in median (1st–3rd quartile).

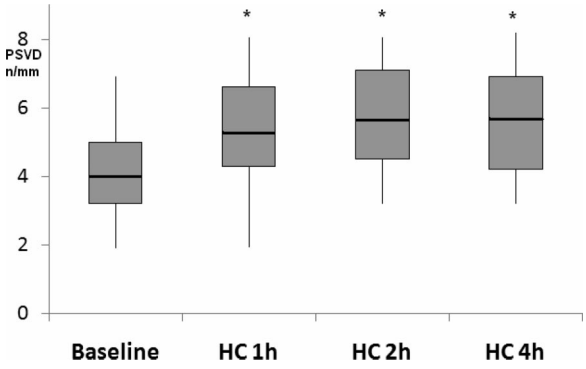

Figure 2. Evolution of microcirculation variables during study time periods. Perfused small vessels density (*PSVD*) (*$p < 0.05$ compared with baseline). *HC*, hydrocortisone.

2). However, MAP increased by >5 mm Hg in ten patients and norepinephrine doses were reduced by >0.1 μg/kg/min in five, so that one can say that hydrocortisone increased vasomotor tone in 12 patients. On the other hand, two patients got worse, with a decrease in MAP and/or an increase in norepinephrine doses.

In contrast to our expectations, we observed a slight but consistent increase in the density of perfused vessels and the density of perfused small vessels (Fig. 2.) already 1 hour after hydrocortisone administration, which was maintained at 2 and 4 hours. This increase in the density of perfused vessels was due to combined increases in small vessel density and an even greater increase in the proportion of perfused small vessels, which counts only the well-perfused small vessels (Table 3). The median change in proportion of perfused vessels between baseline and the mean value at 1, 2, and 4 hours was 11% (5–13). In 13 of the 20 patients, this increase was >10%. The perfusion of large vessels, as expected, was not affected (Table 3). At 24 hours, only 13 patients were investigated as two patients died between 4 and 24 hours and because weaning from mechanical ventilation (but persistent hypoxemia requiring oxygenation with face mask or continuous positive airway pressure) prevented evaluation of the microcirculation in five patients. In the 13 evaluable patients, we observed a persistence of the effect, but only the density of perfused small vessels achieved statistical significance ($p = 0.04$ vs. baseline).

An ACTH test was performed in 13 patients, identifying eight responders and five nonresponders, with median basal cortisol concentrations of 24 (21–26.5) μg/mL and 44 (23–67) μg/mL, respectively. In these 13 patients, microcirculatory variables were similar before the ACTH test compared with baseline values (proportion of perfused small vessels 77 [62–81] and 71 [67–84]% before and after ACTH, respectively, p = not significant). The difference between the two times was 4 (1–8)%, representing a coefficient of variability of 5% (Table 4). We observed no difference in the evolution of microcirculatory variables during hydrocortisone administration between responders and nonresponders to the ACTH test (Fig. 3).

To ascertain that spontaneous evolution of the patients was not responsible for the reported changes during hydrocortisone administration, we also evaluated whether changes in microvascular perfusion during hydrocortisone administration could be related to changes between the two baselines. The average change in proportion of perfused small vessels during hydrocortisone administration was not related to the change in this variable between the two baselines (Fig. 4).

Finally, we also evaluated whether these changes may be affected by global hemodynamic changes. There was no relationship between changes in proportion of perfused small vessels and changes in MAP or cardiac index (data not shown). However, the changes in microvascular perfusion were inversely related to baseline perfusion (Fig. 5).

DISCUSSION

This study demonstrates that the administration of hydrocortisone in septic shock patients results in a discrete, but significant, improvement in microcirculatory variables, independent of changes in global hemodynamic variables.

The mechanisms accounting for this microvascular improvement are largely speculative. A first possibility is that hy-

Table 3. Microcirculatory variables

	Baseline	Hydrocortisone 1 hr	Hydrocortisone 2 hrs	Hydrocortisone 4 hrs
Vessel density—total (n/mm)	7.1 (6.4–7.7)	8.3 (7.4–9.1)	8.6 (8.3–9.7)	8.6 (8.0–9.5)
Perfused vessel density—total (n/mm)	5.7 (4.8–6.4)	7.2 (6.5–9.0)	7.8 (7.2–9.0)	8.0 (7.0–9.0)
Small vessel density (n/mm)	5.2 (4.6–6.2)	6.0 (5.1–7.5)	6.3 (5.5–8.0)	6.5 (5.3–7.8)
Small vessel perfused density (n/mm)	4.0 (3.2–5.0)	5.3 (4.3–6.6)	5.7 (4.5–7.1)	5.8 (4.2–6.9)
% of perfused total vessels	82.1 (68.7–88.0)	89.2 (83.4–92.6)	90.4 (84.6–93.8)	90.4 (87.5– 93.4)
% of perfused small vessels	80.0 (65.9–86.2)	86.5 (80.6–91.1)	87.7 (80.0–92.9)	88.0 (80.7–92.5)
% of perfused large vessels[a]	94.1 (81.4–97.2)	96.7 (90.5–97.6)	95.4 (92.3–97.9)	96.4 (93.1–97.3)

All data presented in median (1st–3rd quartile); all p values <0.01 comparing with baseline except [a]$p = 0.12$, 0.1, and 0.07 for 1, 2, and 4 hrs, respectively.

Table 4. Intrinsic variability of measurements because of spontaneous changes occurring in the 90 min separating the measurements performed before adenocorticotropic hormone (ACTH) test and baseline

	Absolute Difference	Variability (% of Mean)
Vessel density total	0.6 ± 0.6 (n/mm^3)	8.2 ± 8.3
Perfused vessel density total	0.5 ± 0.4 (n/mm^3)	8.6 ± 6.1
Small vessel density	0.6 ± 0.6 (n/mm^3)	10.3 ± 9.9
Small vessel perfused density	0.5 ± 0.6 (n/mm^3)	10.7 ± 9.8
% of perfused small vessels	4.9 ± 4.4 (%)	7.0 ± 6.4

Data calculated in 13 patients in whom an ACTH test was performed before baseline measurements. Data presented as mean ± standard deviation.

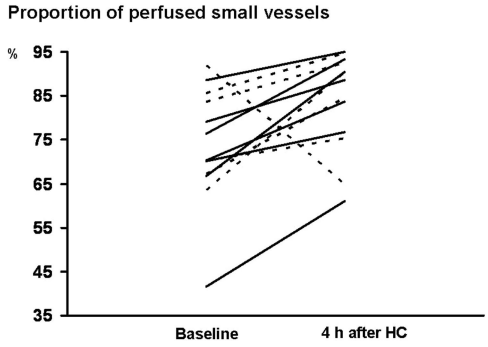

Figure 3. Evolution of proportion of perfused small vessels in adenocorticotropic hormone test responders (n = 8, *plain line*) and nonresponders (n = 5, *dotted line*) (p = not significant). *HC*, hydrocortisone.

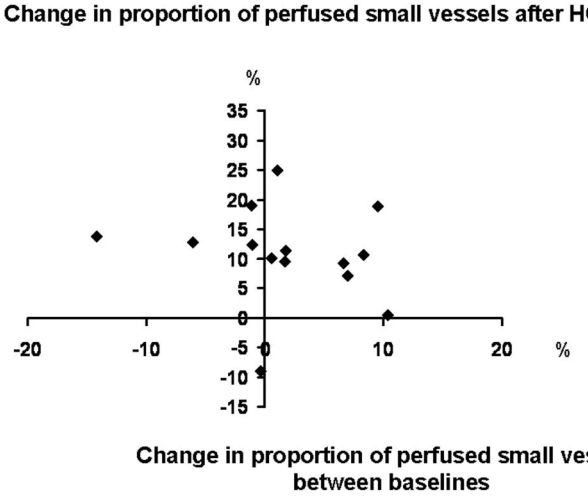

Figure 4. Relationship between changes in microvascular perfusion in response to hydrocortisone (*HC*) and spontaneous changes between the two baselines. In the 13 patients who were tested with adenocorticotropic hormone, the average changes in proportion of perfused small vessels was not related to spontaneous changes during adenocorticotropic hormone test ($r^2 = .03$, $p = 0.53$).

drocortisone interferes with the adrenergic control of the vasculature. Experimental and clinical studies have shown that corticosteroids can restore vascular responsiveness to catecholamines in septic shock (14, 27, 28), leading to a shorter duration of septic shock (11, 13, 19, 29). In this study, we observed that vasomotor tone increased in the majority of the patients, as reflected by an increase in MAP and/or a decrease in norepinephrine requirements. A direct effect of hydrocortisone on the microcirculation is unlikely even though hydrocortisone may increase the number or sensitivity of alpha-adrenergic receptors in the circulatory system, as adrenergic receptors are lacking in the microcirculation. In patients with severe sepsis and septic shock, we previously showed that the microcirculatory alterations were similar in patients treated or not with vasopressor agents (3). An indirect effect, due to an increase in perfusion pressure, may also be considered. In severely hypotensive animals with septic shock, norepinephrine administration failed to affect microvascular blood flow, despite a major increase in MAP from 46 to 71 mm Hg (30). In this study, the changes in microvascular perfusion were not related to the changes in MAP. This is in line with our previous observations showing that changes in microvascular perfusion are independent of global hemodynamic changes during dobutamine administration (8).

A second possibility could be an interaction with the inflammatory response in the microvasculature. Endothelial dysfunction and leukocyte rolling and adhesion are implicated in the microcirculatory alterations seen in inflammatory states (31). Pretreatment with dexamethasone and/or cortisol inhibited the leukocyte adhesion and the intercellular adhesion molecule-1 expression on lipopolysaccharide-stimulated human umbilical vein endothelial cells (32). In experimental models of sepsis, steroid

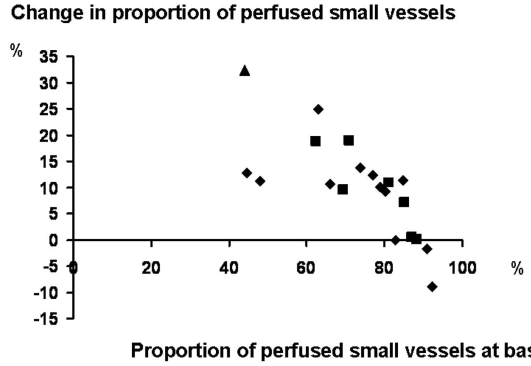

Figure 5. Relationship between microvascular response to hydrocortisone and baseline microvascular perfusion: the evolution of proportion of perfused small vessels is inversely proportional to baseline microvascular perfusion ($Y = -0.47 \times +44$, $r^2 = .55$, $p = -<0.001$). This response was not related to the evolution of vascular tone. Patients are separated according to their hemodynamic response to hydrocortisone: improved (*squares*), unchanged (*circles*), or decreased (*triangles*) vascular tone after hydrocortisone administration.

pretreatment also prevented endothelial expression of adhesion molecules, and leukocyte adhesion and rolling in postcapillary venules (33–35). Circulating cells can also be implicated in the response, because dexamethasone prevented the expression of adhesion molecules on neutrophils (36, 37). Unfortunately, we cannot measure leukocyte rolling and adhesion with orthogonal polarization spectral images so that we cannot confirm or exclude this hypothesis.

Finally, hydrocortisone may modulate nitric oxide (NO) production. Steroids can directly or indirectly inhibit the expression of inducible NO synthase on its transcriptional pathway (38), but may also increase NO production by endothelial NO synthase (39). NO can decrease leukocyte rolling and adhesion to the endothelium (40, 41) and has been shown to improve the microcirculation in small animals (30) and in patients with septic shock (6). Without local NO measurements in our study, we cannot confirm whether this mechanism was involved or not.

Importantly, the effects of hydrocortisone on the microcirculatory alterations were already seen in our study after just 1 hour of hydrocortisone administration, but this does not allows to highlight which mechanism may be involved in the microvascular effects of hydrocortisone. The inhibition of cell adhesion and control of inflammation related to genomic mechanisms that take time and are unlikely to have played a role in the rapid changes observed here. However, some of the effects could be mediated by mechanisms that do not depend on gene regulation, steroids may influence the conformational structure of cell adhesion molecules, which are expressed at the surface of leukocytes in a low-binding state but are susceptible to change rapidly into binding avidity in the presence of inflammatory products (42). In cataract surgery, hydrocortisone treatment 15 minutes before surgery decreased leukocyte rolling and extravasation into the conjunctiva (43). Hemodynamic changes can also occur very rapidly (20, 44). In patients with septic shock, the improved response to norepinephrine (20) and the improvement in cardiovascular variability (44) were already observed 1 hour after hydrocortisone administration. In our study, the global hemodynamic improvement was also observed within 1 hour in most patients.

The effects on the microcirculation were unrelated to the results of the ACTH test. Likewise, Morel et al (29) found that the hemodynamic improvement after hydrocortisone replacement was not associated with the presence or not of relative adrenal insufficiency using several definitions, which is in concordance with the recent results of the CORTICUS trial (13).

Our study has some limitations. First, we did not include a control group because at the time the study was conducted, the Surviving Sepsis Campaign guidelines (12) recommended hydrocortisone administration in septic shock, so we felt it was unethical to randomize patients to a placebo. However, microvideoscopy measurements before the ACTH test were similar to those obtained 90 minutes later, at the time of baseline measurements just before hydrocortisone administration, suggesting that the improvement in the microcirculation observed already 1 hour after hydrocortisone administration was due to the drug and not to a spontaneous evolution. This allowed us to calculate the spontaneous variability of measurements (Table 4), and the changes induced by hydrocortisone were higher than spontaneous changes in all the measured variables. Second, an ACTH test was available only in 13 of 20 patients either because etomidate had been administered or because the attending physician considered that hydrocortisone administration could not be delayed. Third, this study mostly focused on short-term effects of hydrocortisone. Data from only 13 patients were available at 24 hours. Accordingly, significance was lost for many comparisons, but the trends were maintained. We should nevertheless be very cautious in the interpretation of changes at 24 hours, as these patients received three doses of hydrocortisone and, more importantly, other factors may have influenced the microcirculation over this period of time. Confirmation of these findings would require a larger population and a control group. Fourth, other interventions may have influenced the microcirculation (8–10, 45). Importantly, however, none of these were initiated or stopped during the observational period, with the exception of initiation of DAA in one patient and excluding this patient did not alter the results. Fifth, most of our patients were male or postmenopausal women. Estrogen receptors are present in endothelial cells, in capillaries (46), and estrogen administration improves endothelial function, facilitating vasodilation, decreases adhesion molecule expression, and decreases leukocyte adhesion. Some of these effects are mediated through endothelial NO synthase (47). We cannot rule out that our data were not, at least in part, influenced by the hormonal status of these patients. Finally, the alterations we reported were slightly less severe than alterations presented at baseline in other studies (3, 4, 6) using the same method of evaluation. One reason for these findings could be the fact that our patients were already resuscitated with fluids, vasopressors, and dobutamine.

What are the implications of these findings? The improvement in microvascular perfusion was relatively modest, even though statistically significant. The consistency in the changes in microvascular perfusion (two baseline measurements and several times with hydrocortisone) rules out a spurious effect caused by variability in measurements. However,

the magnitude of these changes was quite variable, and an absolute change in proportion of perfused small vessels >10% (representing two times the spontaneous variability between two baseline measurements) occurred in slightly more than half of the patients. We also showed that the improvement in microvascular perfusion was more likely in patients with the more severe microvascular alterations at baseline, which is in line with the effects of other interventions, such as red blood cell transfusions (10). Even though we previously reported that survivors of septic shock experienced microvascular improvements, it would be unwise to recommend routine use of hydrocortisone to improve the microcirculation. Indeed, steroids may increase the risk of recurrent septic shock (13) that may counterbalance the initial positive hemodynamic effects. Accordingly, mortality may not be affected by hydrocortisone administration even though resolution of shock was hastened (13). Nevertheless, recent update of sepsis guidelines suggests that hydrocortisone should be used in the most severe patients (48). If used in these patients, our results clearly show that hydrocortisone does not impair microvascular perfusion.

CONCLUSION

The administration of moderate doses of hydrocortisone in early septic shock resulted in a modest but consistent improvement in capillary perfusion. The improvement was seen already in the first hour after administration of hydrocortisone. The changes in microvascular perfusion were not influenced by the response to an ACTH test. The mechanisms underlying the effects of steroids on the microcirculation need to be elucidated.

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