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ORIGINAL

Development of a septic shock experimental model oriented at training. Application in the training of depuration techniques in the management of severe sepsis

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KEYWORDS
Septic shock;
Extracorporeal depuration;
Animal research

Abstract
Objective: To define a septic shock experimental model that can be used in for training in the early management of septic shock, specifically by extracorporeal depuration (ECD).
Design: A case-control experimental study.
Setting: Veterinary university hospital.
Subjects: Ten Beagle dogs (weight 12-15 kg).
Interventions: Shock was induced using 1 mg/kg *Escherichia coli* lipopolysaccharide (LPS) diluted in 20 mL saline infused in 10 minutes, with a subsequent follow-up at 6 hours. There was no intervention in 5 animals in order to define the natural course of the shock and 5 underwent high volume hemofiltration (HVHF, 100 mL/kg/h) to define delay in response to treatment.
Variables: Pressures (arterial and pulmonary), hemodynamic parameters, gastric tonometry and respiratory function were recorded.
Results: The LPS effect was evidenced at 2 minutes of the infusion and the 10 animals showed severe shock at the end of the infusion. At 2-hours, changes between treated and non-treated animals were seen in cardiac output, systolic volume variability and mucous CO_2. Mean arterial pressure was significantly different at four hours. All non-treated subjects died during the 6-hour follow-up and all the treated animals survived for this period. Based on these results, we developed a workshop that has been used in five courses (www.ccmijesususon.com – www.crrtcordoba.com.es/), obtaining the previous results.
Conclusions: Our shock model shows a predictable behavior, very short latency and a sufficiently rapid improvement in the treated animals for it to be applied in training workshops. It is useful for training in the high-volume hemofilitration (HVHF) and can be used for training in the early management of septic shock.

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PALABRAS CLAVE
Shock séptico;
Depuración extracorpórea;
Experimentación animal

Desarrollo de un modelo experimental de shock séptico orientado a la formación. Aplicación en el entrenamiento de técnicas de depuración en el manejo de la sepsis grave

Resumen
Objetivo: Definir un modelo experimental de shock séptico que pueda aplicarse al entrenamiento en el manejo inicial del *shock* séptico, de forma concreta mediante el uso de técnicas de depuración extrarrenal (TDE).
Diseño: Estudio experimental de casos-control.
Ámbito: Hospital veterinario universitario.
Sujetos: Diez perros Beagle (peso 12-15 kg).
Intervenciones: Se provocó *shock* infundiendo 1 mg/kg de lipopolisacárido de *Escherichia coli* (LPS) en 20 ml salino en 10 min, con un seguimiento posterior de 6 h. Cinco animales no recibieron intervención para definir el curso del *shock* y 5 fueron tratados con hemofiltración de alto volumen (HVHF, 100 ml/kg/h) para valorar la rapidez de respuesta.
Variables de interés: Se monitorizaron presiones (arterial y pulmonar), parámetros hemodinámicos, tonometría gástrica y función respiratoria.
Resultados: A los 2 min el efecto de la infusión de LPS era apreciable y al final de la infusión los 10 animales mostraban *shock* severo. A las 2 h se apreciaban diferencias en gasto cardíaco, variabilidad de volumen sistólico y CO_2 mucoso entre tratados y no tratados. En 4 h la diferencia era evidente también en presión arterial media. Ningún control y todos los tratados sobrevivieron las 6 h del experimento. Posteriormente, hemos desarrollado un taller docente basado en este protocolo que se ha aplicado en cinco cursos de formación (www.ccmijesususon.com; www.crrtcordoba.com.es/), obteniendo los resultados previstos.
Conclusiones: Este modelo de *shock* muestra una respuesta predecible en el tiempo, una latencia muy corta y una mejoría en animales tratados suficientemente rápida como para aplicarlo en talleres de formación. Es útil para el entrenamiento en HVHF y, asimismo, podría aplicarse en otros escenarios de manejo precoz del *shock* séptico.

Introduction

Serious infection is the main cause of multiorgan failure and death in the Intensive Care Unit.[1,2] Different authors have proposed the use of extracorporeal filtration techniques (EFTs) to control or attenuate the response to sepsis and progression towards multiorgan failure. Initially continuous hemofiltration (CHF) was used, followed by more aggressive modalities (high-volume hemofiltration, HVHF), and at present new techniques have been introduced such as those based on adsorption[3-5] or diffusion across high pore density membranes.[6] These technical developments in turn pose a challenge for intensivists in that they are applied to critically ill patients where inadequate utilization can lead to serious consequences. It is therefore important to know the interactions between the EFT employed and the patient life support systems (circulatory, respiratory, etc.), and to ensure adequate training before such techniques are put into practice. However, the learning curve for these techniques is complicated particularly by the limited number of cases in which such techniques are applied within this specific clinical scenario, even though their use in patients with renal failure is very widespread.[7-9]

Lastly, although EFTs are generally considered safe and with a low risk profile, the gradual changes in the way in which they are used have led to an increase in the number of resulting complications – and this potential risk is significantly higher on elevating the treatment dose.[10] Thus, with a view to ensuring patient safety, it is particularly important to develop effective training methods in these highly complex and infrequently used techniques. This concern is reflected by an increasing demand on the part of the professionals for theoretical-practical training courses in the use of EFTs.

We consider that the availability of a teaching model simulating the characteristics of the unstable patient could serve two purposes: (a) to prepare intensivists for the safe use of EFTs in critical patients; and (b) to afford training in the use of techniques specifically targeted to septic patients – all without placing real patients at risk. In this context, the present study describes a model of septic shock which could be adequate for practical training in the use of EFTs in unstable patients.

Material and methods

An experimental study was carried out in two phases: (a) a first phase involving all the animals included in the study, in which septic shock was induced with the purpose of defining the characteristics of shock induction (duration 10 min.); and (b) a second phase following shock induction (duration 6 hours) in which the subjects were divided into two groups – one without intervention measures (sepsis or control group), to define the natural course of shock, and the other subjected to HVHF (HVHF group), to analyze the promptness of response to treatment. The study was carried out in the experimental

LPS = E. coli lipopolysaccharide; MAP = mean arterial pressure; CO = cardiac output; SVR = systemic vascular resistance; dPmax = left ventricle contractility index; SVV = systolic volume variation; VO_2 = oxygen consumption.

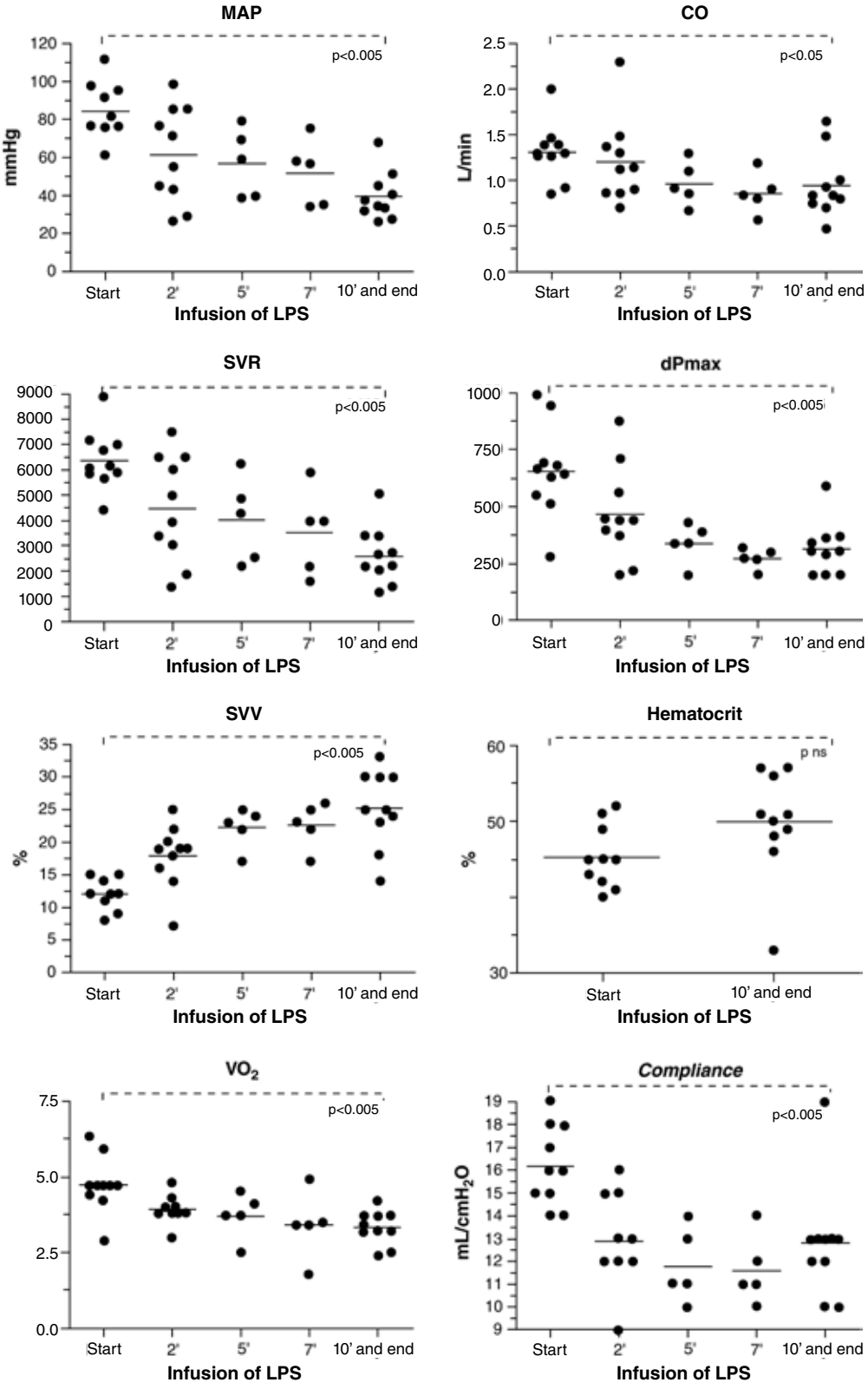

Figure 1 Evolution of the main parameters during the induction of septic shock.

operating room of the Veterinary Hospital of the University of Córdoba (Spain), under control by the anesthesia team of this center, and included ten Beagle dogs (10 in the septic shock induction phase, and 5 in each of the two groups of the follow-up phase) weighing between 12-15 kg.

Anesthesia protocol: The usual anesthetic procedure in this center was used, based on gas anesthesia, relaxation with atracurium, and mechanical ventilation to secure normocarbia. The only volume administration allowed was replacement in all 10 animals of sodium chloride at a rate of 10 ml/kg/h, independently of the clinical condition, and no other treatment was applied during the study.

Monitorization: All dogs were monitored using a Picco® catheter inserted in the femoral artery, a pulmonary artery catheter in the jugular vein, a gastric tonometric probe, a probe for measuring exhaled CO_2, computed calculation of O_2 consumption, and a bladder catheter. In the case of the animals in the HVHF group, a 12 Fr high-flux catheter (Hospal®) measuring 20 cm in length was placed in the other jugular vein. The following parameters were recorded every 15 min. in all subjects: mean arterial pressure (MAP), central venous pressure (CVP), pulmonary artery pressure (PAP), pulmonary capillary (wedge) pressure (PCP), continuous cardiac output (CO), systolic volume variation (SVV) and left ventricle contractility index (dPMax), with calculation of the systemic (SVR) and pulmonary vascular resistances (PVR). We also monitored oxygen consumption (VO_2), end-tidal CO_2 (CO_2-et) and intramucosal CO_2 (CO_2-i). FiO_2, tidal volume (Vol-T), PEEP and pulmonary compliance were recorded. A total of 256 measurements of each study variable were made.

Laboratory tests: Blood was collected at baseline, at the end of sepsis induction and every 30 min. for complete blood counts and arterial blood gas determinations (with calculation of PaO_2/FiO_2).

Induction of sepsis: Under anesthesia, monitoring and stable conditions, the pulmonary lumen of the pulmonary artery catheter was used to infuse a dose of 1 mg/kg/b.w. of an ultrapure lipopolysaccharide preparation of *Escherichia coli* (strain 0111:B4) (InvivoGen®) (LPS) in fixed dilution in all the animals (20 ml at a rate of 2 ml/min, with a total duration of infusion of 10 min.). All the subjects received the full dose in the predetermined period of time. After induction, follow-up was carried out during 6 hours of all dogs (both groups), after which the survivors were sacrificed according to the norms of the Veterinary Hospital.

The sepsis group was monitored without intervention, while in the HVHF group treatment was started 15 min. after completing the infusion of LPS.

HVHF protocol: AN69 membrane 0.9 m^2 using a Prisma® monitor, with blood flow of 130 ml/min., hemofiltration dose 100 ml/kg/h, extraction 0, anticoagulation with non-fractionated heparin (15 U/kg/h) and fluids with bicarbonate. Temperature was maintained by means of an external heater with a water bath, and applying heat sources to the subjects. The treatment was started 15 min. after the induction of sepsis, and at the time of connection we simultaneously administered 1 ml/kg of hydroxyethyl starch (Voluven®) to compensate the loss caused by the circuit volume (approximate priming volume 80 ml).

Ethical considerations: The study was approved by the Ethics Committee of the Veterinary Hospital of the University of Cordoba.

Statistical analysis: The SPSS version 11 statistical package for MS Windows was used. The data are presented as the mean ± standard error of the mean or as percentages. Comparisons were made with the Mann-Whitney U-test for dichotomic variables, and with the Kruskal-Wallis test when the variables presented more than two possible values. Statistical significance was accepted for $p<0.05$ in all cases.

Table 1 Evolution of the main variables monitored during the infusion of LPS in all the study subjects (sepsis group and HVHF group)

	Baseline	2 minutes	5 minutes	7 minutes	10 minutes	P[a]
MAP *mmHg*	84.6 ± 4.6	61.6 ± 8.0	57.1 ± 8.1	51.9 ± 7.8	39.6 ± 4.1	*< 0.005*
HR *bpm*	100 ± 2.9	98 ± 3.8	94 ± 1.8	92 ± 1.3	95 ± 2.7	*< 0.05*
CO *l/min*	1.3 ± 0.1	1.2 ± 0.1	0.9 ± 0.1	0.8 ± 0.1	0.9 ± 0.1	*ns*
SVR *dynes*	6.386 ± 371	4.507 ± 666	4.028 ± 745	3.536 ± 755	2.627 ± 356	*< 0.005*
SVV *%*	12 ± 0.7	18 ± 1.5	22 ± 1.4	23 ± 1.6	25 ± 1.9	*< 0.005*
dPmax	658 ± 64	466 ± 65	340 ± 39	273 ± 20	316 ± 37	*< 0.005*
CVP *mmHg*	5.8 ± 0.9	5.5 ± 0.6	5.8 ± 1.1	5.8 ± 1.0	5.5 ± 0.6	*ns*
mPAP *mmHg*	11.2 ± 0.9	-	-	-	13.3 ± 1.6	*ns*
PCP *mmHg*	7.0 ± 0.8	-	-	-	6.8 ± 1.1	*ns*
PVR *dynes*	270 ± 41	-	-	-	295 ± 45	*ns*
VO_2 *ml/min*	4.7 ± 0.3	3.9 ± 0.1	3.7 ± 0.3	3.4 ± 0.5	3.3 ± 0.2	*< 0.005*
CO_2i *Kpc*	6.5 ± 0.5	6.7 ± 0.4	6.3 ± 0.6	5.9 ± 0.7	6.8 ± 0.4	*ns*
Temperature	35.9 ± 0.5	35.8 ± 0.5	34.8 ± 0.8	34.6 ± 0.9	35.7 ± 0.6	*ns*
$SatO_2$%	96.8 ± 0.5	96.4 ± 0.8	95.8 ± 1.0	94.2 ± 1.4	96.5 ± 0.6	*ns*
Compliance	16.0 ± 0.6	12.9 ± 0.6	11.8 ± 0.7	11.6 ± 0.7	12.8 ± 0.8	*< 0.005*

[a]With respect to baseline. The data are presented as the mean ± standard error of the mean; the missing pulmonary pressure data are due to the suspension of measurement during the infusion of LPS. MAP = mean arterial pressure; HR = heart rate; CO = cardiac output; SVR = systemic vascular resistance; SVV = systolic volume variation; dPmax = left ventricle contractility index; CVP = central venous pressure; mPAP = mean pulmonary artery pressure; PCP = pulmonary capillary pressure; PVR = pulmonary vascular resistance; VO_2 = O_2 consumption; CO_2i = intramucosal CO_2; $SatO_2$ = O_2 saturation.

Table 2 Differences in the evolution of the different variables during the follow-up period (360 min.) between the treated group (HVHF) and the control group (sepsis)

Variable/Group	End of LPS infusion	60'	120'	180'	240'	300'	End
MAP mmHg*							
HVHF	40.7 ± 5.2	54.1 ± 5.0	47.9 ± 3.6	49.2 ± 4.4	60.1 ± 5.1	66.1 ± 5.0	66.8 ± 10.8
Sepsis	35.5 ± 4.2	39.0 ± 4.5	35.5 ± 4.2	37.5 ± 4.8	38.3 ± 8.7	33.8 ± 10.2	29.3 ± 6.0
CO l/min*							
HVHF	1.1 ± 0.1	1.7 ± 0.2	1.8 ± 0.2	1.8 ± 0.3	1.7 ± 0.3	1.6 ± 0.3	1.5 ± 0.3
Sepsis	0.7 ± 0.1	0.9 ± 0.1	0.9 ± 0.1	1.0 ± 0.3	0.8 ± 0.1	0.8 ± 0.2	0.8 ± 0.1
SVR Dynes*							
HVHF	2.593 ± 430	2.449 ± 409	2.084 ± 310	2.117 ± 241	2.783 ± 282	3.535 ± 474	3.614 ± 735
Sepsis	3.296 ± 428	3.325 ± 669	2.889 ± 667	3.090 ± 617	3.312 ± 618	3.042 ± 893	2.596 ± 516
SVV %*							
HVHF	23.8 ± 4.1	18.6 ± 2.8	24.2 ± 1.0	22.0 ± 2.3	19.2 ± 3.8	19.6 ± 4.2	16 ± 3.2
Sepsis	26.8 ± 1.3	28.0 ± 2.3	27.0 ± 2.3	28.0 ± 2.0	27.0 ± 3.5	25.0 ± 5.9	26.8 ± 2.9
*dPmax**							
HVHF	347 ± 89	659 ± 186	499 ± 81	492 ± 84	567 ± 90	592 ± 99	530 ± 85
Sepsis	302 ± 28	383 ± 37	413 ± 49	401 ± 83	346 ± 49	245 ± 20	238 ± 13
mPAP mmHg							
HVHF	9.4 ± 1.3	10.1 ± 1.4	10.9 ± 1.7	9.9 ± 1.7	10.5 ± 1.8	10.7 ± 1.8	10.6 ± 1.5
Sepsis	13.5 ± 1.1	10.3 ± 1.2	9.5 ± 0.9	9.3 ± 0.5	8.6 ± 1.8	9.6 ± 2.0	9.2 ± 1.1
PVR Dynes							
HVHF	280 ± 39	200 ± 29	256 ± 60	213 ± 51	300 ± 76	284 ± 91	274 ± 77
Sepsis	310 ± 116	399 ± 101	298 ± 59	362 ± 94	389 ± 55	495 ± 102	435 ± 70
VO_2 ml/min*							
HVHF	3.6 ± 0.2	3.9 ± 0.3	4.5 ± 0.3	3.9 ± 0.1	4.5 ± 0.2	4.1 ± 0.1	3.7 ± 0.1
Sepsis	2.9 ± 0.2	4.0 ± 0.4	4.6 ± 0.6	4.2 ± 1.2	4.1 ± 1.1	3.9 ± 1.6	3.1 ± 1.0
Kpa							
HVHF	7.3 ± 0.6	8.4 ± 0.2	8.7 ± 0.2	8.9 ± 0.5	9.2 ± 0.7	9.5 ± 1.2	9.6 ± 1.5
Sepsis	6.6 ± 0.6	10.2 ± 1.1	13.7 ± 2.2	15.2 ± 2.6	14.9 ± 2.5	14.2 ± 2.6	14.5 ± 1.3
Compliance ml/cmH_2							
HVHF	14.4 ± 1.2	14.2 ± 0.4	14.0 ± 0.5	14.6 ± 0.2	13.6 ± 0.2	13.4 ± 0.2	13.8 ± 0.6
Sepsis	11.4 ± 0.6	12.6 ± 0.4	12.6 ± 0.2	12.0 ± 0.3	11.3 ± 2.1	11.0 ± 0.6	11.2 ± 0.5
Base defect meq							
HVHF	−9. 0 ± 1.0	−13.0 ± 0.3	−13.0 ± 1.4	−13.0 ± 0.0	−12.1 ± 0.4	−10.4 ± 1.4	−10.5 ± 3.7
Sepsis	−14.0 ± 1.0	−15.7 ± 0.8	−16.0 ± 1.1	−17.5 ± 2.6	−20.1 ± 4.2	−20.7 ± 1.4	−18.9 ± 3.2
PaO_2/ FiO_2							
HVHF	416 ± 33	495 ± 35	559 ± 24	454 ± 94	559 ± 29	542 ± 90	614 ± 88
Sepsis	487 ± 75	457 ± 74	464 ± 81	485 ± 91	434 ± 29	443 ± 129	461 ± 94

All data are presented as the mean ± standard error of the mean; *p < 0.05 at the end of follow-up. MAP = mean arterial pressure; HR = heart rate; CO = cardiac output; SVR = systemic vascular resistance; SVV = systolic volume variation; dPmax = left ventricle contractility index; CVP = central venous pressure; mPAP = mean pulmonary artery pressure; PCP = pulmonary capillary pressure; PVR = pulmonary vascular resistance; VO_2 = O_2 consumption; CO_2i = intramucosal CO_2; $SatO_2$ = O_2 saturation.

Results

Severe septic shock was induced in all the animals (characterized by a rapid drop in MAP and CO, and elevation of SVV) (Table 1) before completing the infusion of LPS, though none of them died in this phase of the experiment. Shock proved evident in most of the subjects between 2-5 min. after starting the infusion (Fig. 1).

The HVHF technique was carried out without problems except for early coagulation of a single filter that implied the loss of 15 min. of that treatment.

The posterior course proved similar during the first two hours of follow-up, with maintenance of the situation of hypoperfusion (critical MAP, low CO, elevated SVV and diminished VO_2 and CO_2-i) (Table 2). However, starting from this timepoint, a positive effect was seen in the evolution of the HVHF group, with moderate but progressive improvement in blood pressure, CO, SVV and SVR, that persisted up until the end of the protocol. In contrast, in the untreated sepsis group the situation of severe shock persisted up until the end of follow-up (Fig. 2).

Regarding survival, all the animals in the sepsis group died during follow-up (one after 150 min, another after 250 min., a third after 315 min, and the remaining two before 360 min), with a median survival of 288 ± 39.5 min. All the animals in the HVHF group survived this period.

Discussion

We have presented an experimental model of septic shock that may prove very adequate for application in training workshops for the learning of extracorporeal filtration techniques (EFTs). The model is reproducible, with a very rapid and well defined response, and allows the animal to survive long enough to be able to detect changes secondary to treatment – thereby in principle proving adequate for acquiring skills in the application of EFTs to critically ill

The bars represent the mean ± standard error of the mean. HVHF = high volume hemofiltration; MAP = mean arterial pressure; dPmax = left ventricle contractility index; SVV = systolic volume variation.

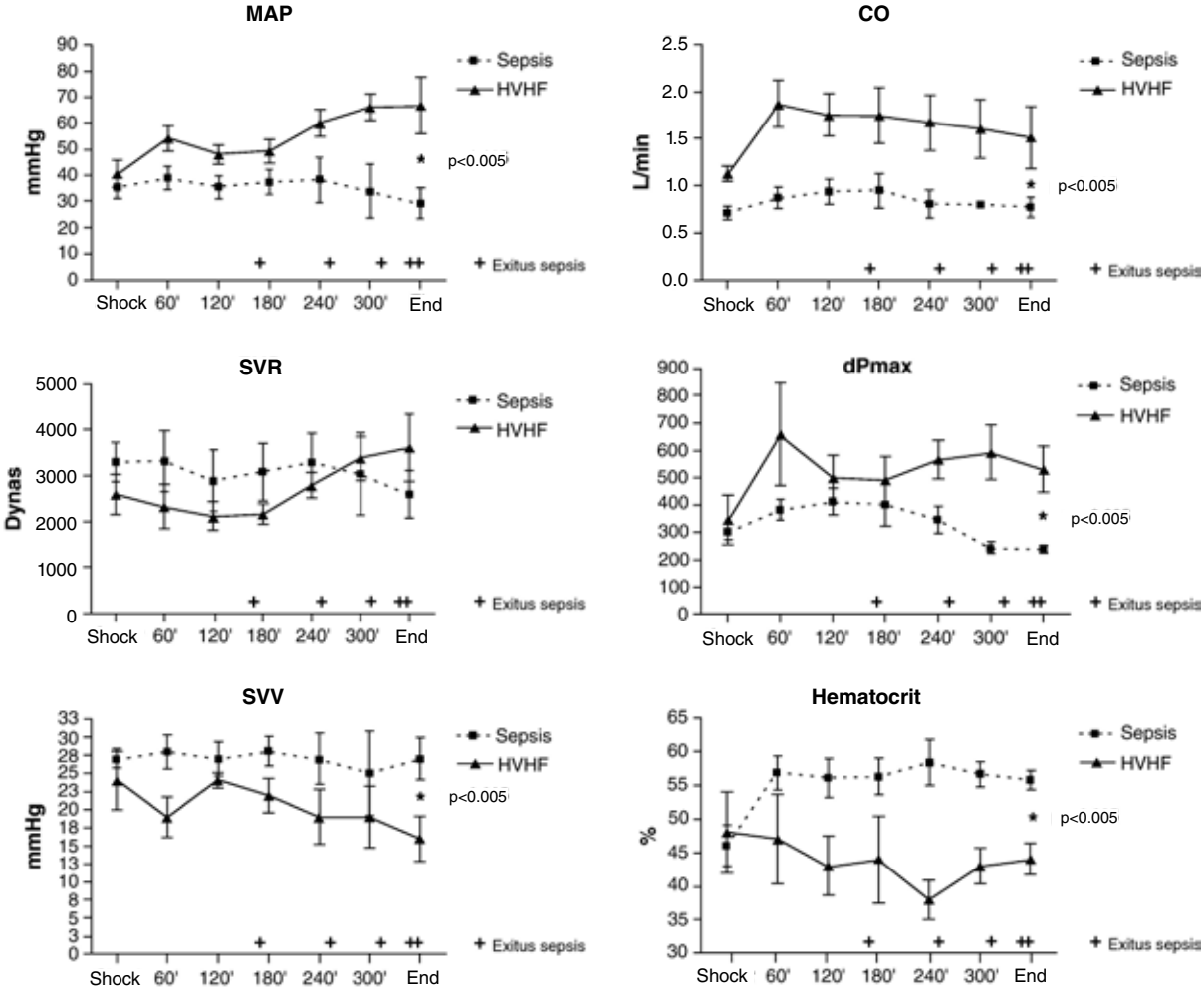

Figure 2 Evolutive differences between the treated and non-treated animals.

patients. The study was carried out under experimental conditions; based on the results obtained, it therefore proved necessary to posteriorly evaluate the applicability of the model. To this effect we have designed a workshop model based on the use of multimedia support so that all participants can continuously follow the evolutive changes occurring during the induction of septic shock. Posteriorly, in different groups and on a physical-presence basis, HVHF is applied in a real life scenario, with follow-up of its effects over time. To date, this model has been used in five editions of theoretical-practical training courses on renal filtration techniques (http://www.ccmijesususon.com; www.crrtcordoba.com.is/), and in all of them it has shown the planned performance – making it possible to adequately cover the training objectives. We moreover feel that this model could also be used in other scenarios such as training in the initial management of septic shock or in advanced monitorization interpretation skills.

The use of animal models in application to EFT training has been a reality in Spain since the introduction in 1999 of a theoretical-practical course imparted in the CCMI of Cáceres, based on workshops in which different EFT modalities are applied to experimental animals. The growing demand for participation in courses of this kind shows that they are viewed as necessary for effective training of the specialists that use such techniques. The possibility of simulating "real patient" management in these workshops is reinforced by allowing the intensivist to deal with an individual in severe septic shock requiring filtration therapy.

Animal experimentation models have been intimately linked to the development of EFTs, and even more so to the application of such techniques in the management of sepsis. From the start of their use, studies appeared describing animal models of sepsis and pointing to possible short-term benefits in terms of the hemodynamic profile and oxygenation after continuous hemofiltration (CHF). In 1990, Stein et al.[11] published a study in pigs weighing 28-32 kg in which shock was induced using *E. coli* lipopolysaccharide (LPS) in continuous infusion. The authors started with 2 µg/kg/h and increased the dose every 10 min until an appreciable hemodynamic and respiratory effect was obtained (this taking almost two hours). At this point they reduced the dose to one-half and maintained it until the end of the experiment. Simultaneously, CHF was started with a replacement rate of 600 ml/h maintained during 6 hours. In this time the authors observed a positive filtration effect reflected in the hemodynamic profile of the animals. This study had some problems, however. In particular, treatment was started before the infusion of LPS; as a result, part of the results may have been conditioned or biased by this fact. On the other hand, the beneficial effects were reached slowly, and the induced shock was not very intense.

A short time later, in 1992, a new study was published by Grootendorst et al.,[12] involving a novel form of using CHF. These authors induced shock in 18 pigs weighing 36-39 kg by infusing LPS at a dose of 0.5 mg/kg over 30 min, after which the animals were randomized to either HVHF at a dose of 6 l/h or no treatment. Septic shock proved clinically evident within 30 min after ending the infusion, and the positive effects of treatment became apparent from the second hour onwards. The most relevant aspect of this study is that it served as the basis for the development of high volume filtration as it is used today – specifically, the high-dose and short duration pulse modality, designed by Honore et al.[13]

The use of LPS also has been described by other authors such as Bellomo et al.,[14] in dogs weighing about 20 kg and subjected to the injection of 0.5 mg/kg in 5 min. Although these authors provided no detailed description of the induction of sepsis, they recorded a positive effect of CHF at a dose of 1750 ml/h in the treated group, and this effect became apparent within approximately 30 min. However, this protocol again presented the problem of starting treatment before LPS administration – thus complicating standardization and the comparison of effects. Furthermore, the latter persisted for only three hours. Similar results have been obtained by other protocols based on similar doses of CHF and LPS; here again the onset of shock proved relatively slow, though with an early positive response to treatment.[15]

Another alternative widely employed in models of sepsis and EFTs involves the use of live bacteria. Specifically, the infusion of *E. coli* colony forming units (CFUs) has been the model chosen by different authors.[16,17] However, while this approach more closely reproduces the situation found in human patients, it poses the important disadvantage of a slower onset of septic shock (between 1-6 hours), and is therefore less predictable. This makes the model less useful for teaching purposes, where more precise programming of the start of effect is needed.

Probably the models best suited for studying the effects of septic shock or its treatment are those based on the induction of peritonitis, since they more closely reproduce the disease process found in humans. However, the multiple studies published to date with this model[18-20] report an excessively slow onset of effect – thereby making it completely unacceptable in the teaching scenario.

There are clear time limitations in the teaching scenario that make it necessary to be able to precisely define the time to appearance of the symptoms (this having to coincide with the start of the working session), and of course the development of important changes must be appreciable within the course of the working session. This cannot be achieved with models based on live microorganisms, which have been shown to be inoperative in this sense. Models based on the use of LPS therefore appear as the best option for application in training workshops – though to date the published studies generally report a somewhat slow onset of effect (albeit not as slow as in the models based on live germs). In this respect, the model published by Grootendorst[12] comes closest to satisfying the needs which we had established in our study, and served as the basis for our own model - with the introduction of modifications designed to ensure a faster and more intense effect.

The injection of LPS produces a sharp but transient increase in cytokine levels, while live bacterial infection induces a slow but more sustained increase, with comparatively lesser increments in proinflammatory mediators. In fact, as has been seen from our data, septic shock in the first scenario is hypodynamic, while in the latter scenario (which more closely reproduces the situation found in humans) shock is hyperdynamic.[21] Interestingly, we recorded a very early and intense decrease in intravascular fluid, with marked hypovolemia from the early stages of

shock, which in turn was possibly reinforced by the absence of resuscitation measures in the animals. With the aforementioned important limiting elements, this probably defines the model as being more similar to the situation found in human clinical practice.

In any case, it was not our aim to establish septic shock conditions completely comparable to those found in humans. Rather, we wanted to establish a series of defined hemodynamic alterations allowing us to clearly evidence the repercussion (positive or negative) of extracorporeal filtration upon the altered study parameters. On the other hand, all animal models of sepsis show differences in terms of the type of alteration, duration and intrinsic response, depending on the species involved, and therefore cannot be taken to reproduce sepsis seen in humans.[22] Taking this into account, while it is true that models based on LPS are less representative of the situation found in humans than models based on live microorganisms, the hemodynamic alterations produced by LPS are reproducible and predictable, they make it possible to monitor treatment response, and in particular they present latency intervals short enough to make them useful for teaching purposes.

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