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Gastric tonometry versus cardiac index as resuscitation goals in septic shock: a multicenter, randomized, controlled trial

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ABSTRACT

Introduction: The goals for septic shock resuscitation remain controversial. Despite the normalization of systemic hemodynamic variables, tissue hypoperfusion can still persist. Indeed, lactate or oxygen venous saturation may be difficult to interpret. Our hypothesis was that a gastric intramucosal pH-guided resuscitation protocol might improve the outcome of septic shock compared to a standard approach aimed at normalizing systemic parameters such as cardiac index (CI).

Methods: 130 septic shock patients were randomized to two different resuscitation goals: CI ≥ 3.0 L/min/m2 (CI group: 66 patients) or intramucosal pH (pHi) ≥ 7.32 (pHi group: 64 patients). After correcting basic physiologic parameters, additional resuscitation consisting in more fluids and dobutamine was started if specific goals for each group had not been reached. Several clinical data were registered at baseline and during evolution. Hemodynamic data and pHi values were registered every 6 hours during the protocol. Primary end-point was 28 days mortality.

Results: Both groups were comparable at baseline. The most frequent sources of infection were abdominal sepsis and pneumonia. Twenty-eight day mortality (30.3 vs. 28.1%), peak Therapeutic Intervention Scoring System scores (32.6 ± 6.5 vs. 33.2 ± 4.7) and ICU length of stay (12.6 ± 8.2 vs. 16 ± 12.4 days) were comparable. A higher proportion of patients exhibited values below the specific target at baseline in the pHi group compared to the CI group (50% vs. 10.9%; $P < 0.001$). Of 32 patients with a pHi < 7.32 at baseline, only 7 (22%) normalized this parameter after resuscitation. Areas under the receiver operator characteristic curves to predict mortality at baseline, and at 24 and 48 hours were 0.55, 0.61, and 0.47, and 0.70, 0.90, and 0.75, for CI and pHi, respectively.

Conclusions: Our study failed to demonstrate any survival benefit of using pHi compared to CI as resuscitation goal in septic shock patients. Nevertheless, a normalization of pHi within 24 hours of resuscitation is a strong signal of therapeutic success and in contrast, a persistent low pHi despite treatment is associated with a very bad prognosis in septic shock patients.

Introduction

The subject of the best resuscitation goal for septic shock is still controversial [1-5]. The early goal directed therapy (EGDT) trial showed that an aggressive resuscitation protocol aimed at normalizing central venous oxygen saturation (ScvO2), may improve patient outcome if started early in the pre-ICU setting [2]. Nevertheless, the very low ScvO2 values in the EGDT trial, contrast with the findings of several ICU studies [6-8]. Moreover, a multicentric Italian study showed no advantage of resuscitating against mixed venous oxygen saturation (SmvO2) > 65% in critically ill patients with up to 48 hours of shock evolution [3]. In addition, physiological interpretation of lactate and central venous oxygen saturation as perfusion parameters may be difficult in some clinical settings and both are not specific or sensitive markers of tissue hypoperfusion [9, 10]. Moreover, it is not clear if perfusion parameters are reliable if pursued late in the ICU setting [3, 8].

In this context, gastric tonometry, a technique that indirectly assesses gastric mucosal perfusion, appears as an attractive alternative. Low gastric intra-mucosal pH (pHi) is a sensitive marker of splanchnic hypoperfusion and a good predictor of poor outcome in critically ill patients [11, 12], but no study specifically testing its potential role as a resuscitation goal in septic shock has been reported.

Ten years ago we conducted a yet unpublished, multicenter randomized controlled study comparing intramucosal gastric pH (pHi) vs. cardiac index (this later as representing macrohemodynamic parameters) as therapeutic objectives in septic shock patients, with the hypothesis that pHi-guided resuscitation may improve survival. (Fernando Palizas, Arnaldo Dubin, Tomas Regueira, Alejandro Bruhn, Elias Knobel, Silvio Lazzeri, Natalio Baredes and Glenn Hernández, unpublished data). Since then, the controversial issue of the best resuscitation goal for septic shock has not been resolved [7, 8] and therefore, we considered as clinically relevant to present our data testing an important physiologic marker of regional perfusion such as gastric tonometry.

Materials and Methods

This study was approved by the Institutional Review Boards of all centers involved. All participants or their relatives signed an informed consent form prior to be enrolled in the

study. The study was conducted from July 1998 through May 2000 in six closed intensive care units from Chile, Argentina and Brazil.

All adult patients fulfilling criteria for septic shock according to the ACCP/SCCM Consensus Conference [13] within 48 hrs of ICU admission were considered and selected if in a 12 hrs time-window. Exclusion criteria were: terminal illness with the patient expected to die within 28 days, irreversible neurological impairment, and contraindication for nasogastric tube placement. Randomization was done by the central coordinator center. All patients were initially treated to normalize macrohemodynamic parameters for 2-4 hrs (figure 1), especially a mean arterial pressure $\geq$ 70 mmHg, and were randomized thereafter to a goal-directed therapy aimed at a gastric mucosal pHi $\geq$ 7.32 (pHi group) or a cardiac index $\geq$ 3.0 L/min/m2 (CI group). This later value was selected to prevent low systemic flow in this group [3]. A pulmonary artery catheter was placed in all patients and additionally, patients assigned to the pHi group, received a gastric tonometer. Measurements of pHi were obtained with a tonometer (TRIP NGS catheter, Tonometrics, Inc., Worcester, MA) consisting of a gas permeable silicone balloon located at the distal end of a conventional nasogastric tube. The silicone balloon is filled with saline, and carbon dioxide diffuses and equilibrates between the mucosa and the saline solution in the balloon to a steady state in 30 to 90 minutes. The solution is sampled anaerobically and adjusted to a steady state carbon dioxide (PCO_2 SS). The measurement of arterial bicarbonate from a simultaneously obtained arterial blood gas sample allows calculation of the pHi using a modified Henderson-Hasselbach equation pHi = 6.1 + log (arterial bicarbonate)/(0.03 x tonometer pCO_2 SS). All patients received H2 receptor antagonists and enteral feeding was avoided throughout the study period.

All patients received initial resuscitation aimed at normalizing macrohemodynamic parameters and to maintain certain clinical variables within physiologic limits as shown in figure 1. Additional steps (mainly fluids to reach a plateau phase in the Starling curve and dobutamine) were taken if the specific goal for each group was not achieved (Figure 1). This hemodynamic management strategy was mandatory for the first 48 hours of the study, and recommended but not required, later. The PAC and tonometer were removed once the resuscitation goal was maintained for 24 hours and if patients were considered stable by the supervising ICU staff.

Several clinical and demographic data including age, sex, cause of sepsis, admission APACHE II (Acute Physiologic and Chronic Health Evaluation) score, and daily SOFA (Sepsis-related Organ Failure Assessment) and TISS scores were registered. Patients were followed for a maximum of 28 days. Hemodynamic data including cardiac index, vasoactive drugs dose, and pHi in the corresponding group were registered every 6 hours.

Statistical Analysis

The primary study endpoint was 28 day mortality. Considering a two-sided type I error rate of 5 percent, and a power of 80 percent, we calculated that a sample size of 128 patients was required to permit the detection of a reduction in ICU mortality from 40 to 20%. Primary analysis was carried out on an intention-to-treat basis; Kaplan–Meier estimates of mortality was used to describe the relative risk of death. Differences between the two groups were assessed with the use of Student's t-test and the chi-square test as corresponded. Receiver operator characteristic (ROC) curves were performed for mortality prediction with pHi and cardiac index values at different time points of resuscitation. Data are presented as mean ± SD. A $p < 0.05$ by a two-tailed test was considered statistically significant.

Results

One-hundred and thirty consecutive patients with septic shock were enrolled and randomly assigned to the CI (66 patients) or pHi groups (64 patients). No differences between groups were found at baseline, except for a higher SOFA score in the pHi group (Table 1). The most common diagnoses were abdominal sepsis in 88 (68%) and pneumonia in 26 patients (20%). Overall, 28 day mortality (30.3 vs. 28.1%; logrank test p=0.98) (Figure 2), peak TISS scores (32.6 ±6.5 vs. 33.2 ± 4.7; p=0.52) and ICU length of stay (12.6 ± 8.2 vs. 16 ± 12.4 days; p=0.07) were comparable. The cumulative survival curves are shown in Figure 2.

A higher proportion of patients exhibited values below the specific target at baseline in the pHi group compared to the CI group (32/64 (50%) vs. 7/66 (10.9%); p<0.001). Of 32 patients with a pHi < 7.32 at baseline, only 7 (22%) normalized this parameter after 24 hrs. of resuscitation and all of these patients survived. The mean values of cardiac

index and pHi at different time points are shown in table 2. We could not demonstrate any difference between CI and pHi groups in the intensity of treatment as reflected by comparable peak TISS scores (32.6 ± 6.5 vs. 33.2 ± 4.7; p=0.52), but there was a trend to more dobutamine use (31.8 vs. 48.4%; p=0.07) and with higher peak doses (8.8±10.6 vs. 13.4±7.8 μg/kg/min; p=0.1) in the pHi group. pHi was a better predictor of outcome than cardiac index (Figure 3).

Discussion

Our study failed to demonstrate any difference in survival of septic shock patients treated with pHi or cardiac index as a guide of hemodynamic resuscitation. Nevertheless, our findings confirm previous reports about the prognostic value of a persistent low pHi [11, 12]. In addition, although only 22% of patients with low admission pHi values normalized this parameter after resuscitation, this fact was associated with a high probability of survival.

This prospective, randomized, controlled study is the first to evaluate the use of pHi as a resuscitation goal specifically in septic shock patients. We hypothesized that septic patients may benefit from organ perfusion-oriented resuscitation, since splanchnic circulation is particularly sensitive to cardio-circulatory changes in sepsis. Changes include a redistribution of blood flow away from the mucosa, constriction of the villus arteriole and microcirculatory derangements [14], which could be associated with hypoxia and to an increase in gut permeability. [15-18]. Why does a physiologically sounded goal fail to demonstrate any benefit when used as a therapeutic objective? There are many possible explanations. First, our study could be underpowered to detect a real difference, but this is unlikely when observing the almost superimposed Kaplan Meier curves. Second, pHi may be a proper goal but only for an earlier stage of septic shock. This factor can strongly influence results as demonstrated by the example of the positive EGDT [2] vs. the negative Italian multicentric [3] trials. Both were aimed at basically the same resuscitation goal (central or mixed venous oxygen saturation). Nevertheless, the former was used very early, in the pre-ICU setting, and the second during late ICU management. Our study was similar in design to the Italian study including patients up to 48 hours of ICU stay. It is possible that during this period patients may have been exposed to prolonged hypoperfusion prior to be randomized. This may have lead to irreversible hypoxia or multiple organ dysfunctions in some

patients. Similarly, Gutierrez et al., showed that pHi-guided resuscitation of critically ill patients was only successful in patients admitted with normal pHi (11). On the other hand, patients with intramucosal acidosis on admission failed to improve their outcome. This finding was ascribed to longer tissue hypoxia in this group.

A third potential factor is the relative ineffectiveness of treatments aimed at normalizing pHi. In fact, no study has unequivocally demonstrated a positive impact of specific therapies such as volume, different catecholamines or vasodilators over gut mucosal perfusion [19, 20]. Dobutamine has a relatively low therapeutic index, could be dangerous when used in high doses [4], and in some cases may be ineffective because unwanted effects (such as tachycardia or arrhythmias) preclude an optimal titration. This fact could explain why both groups used almost comparable doses of dobutamine and exhibited similar cardiac index, despite that more patients in the pHi group were below target at baseline.

Although our study did not show a survival advantage of using pHi-guided resuscitation in septic shock patients, our results are consistent with Gutierrez's [11], and Ivatury's studies [12] demonstrating that patients who reach or maintain a normal pHi after an aggressive resuscitation, have a higher probability of survival.

Although our results could be considered as negative, it is interesting to make some additional considerations. Except for the controversial EGDT trial in early pre-ICU setting, no study so far has convincingly demonstrated an advantage of perfusion-oriented goals (such as lactate or SmvO2) over classic hemodynamic parameters as end-points of resuscitation. Nevertheless, there are many proofs that "normal" hemodynamic parameters (including mean arterial pressure, cardiac index, oxygen transport) can coexist with profound tissue hypoperfusion or microcirculatory derangements [21, 22]. Therefore, the actual standard of care is to resuscitate septic shock patients until normalizing perfusion related parameters such as clinical perfusion, lactate or ScvO2/SmvO2 [1]. One problem with this approach is that both lactate and ScvO2 may be difficult to interpret in some settings (i.e. liver failure, epinephrine use, early after intubation) [8, 9]. Moreover, tissue hypoperfusion can be present in patients with normal ScvO2 [12] Gastric tonometry has been shown to be well correlated with splanchnic perfusion in different models of shock [23-29]. In this context, gastric tonometry may still have a role to assess perfusion and guide resuscitation therapy in

some patients, in whom other markers such as lactate or ScvO2 may be misleading or confusing. A normalization of pHi within 24 hours of resuscitation is a strong signal about therapeutic success and in contrast, a persistent low pHi despite treatment is associated with a very bad prognosis in septic shock patients.

Our study was performed a decade ago. In the mean time, more insight has been gained into several technical and physiologic limitations of gastric tonometry which have precluded its further technological development or clinical acceptance. However, its physiologic rationality has been recently validated in several experimental studies (14-19). Gastric tonometry has also undergone a number of methodologic changes over the last decade, shifting from saline to automated gas tonometry, which incorporates the direct analysis of intraluminal pCO2 and pCO2 gap. One of the potencial pitfalls of pHi calculation is that it includes arterial bycarbonate, which is a systemic parameter not dependent on gut perfusion. Although the use of pCO2 gap instead of pHi is more physiologically sounded [30], we do not believe that this fact would have changed our results. There are some controversial data about the validity of pCO2 gap as a marker of splanchnic perfusion [31-33] and it has not been tested as a resuscitation goal. In addition, there is scarce evidence about its prognostic value [34 and no clinical study has demonstrated its superiority over pHi.

Our study has several limitations. First, the lack of data about fluid balance and SmvO2 may limit the interpretation of our results. Second, the use of cardiac index as a resuscitation goal is questionable since no "normal" values of CI can be recommended for any given clinical condition. Instead, the concept of adequate or inadequate cardiac index should be used, according to the adequacy of flow to real O2 demand [35]. Nevertheless, cardiac index has not been shown to be inferior to other parameters when used as resuscitation goal in the past [3]. Third, more than 60% of our septic patients were of abdominal origin, in contrast to large epidemiologic data that show that lung is the predominant source of sepsis worldwide. Therefore, we cannot assure that our results would have been the same in a larger more typical ICU population.

Despite these limitations we considered important to report this study because: a) the controversy about the best resuscitation goal for septic shock still persists; b) other potential perfusion or metabolic resuscitation goals such as ScvO2 or lactate may be

very difficult to interpret in some settings; c) evolution of pHi after 24 hrs of resuscitation provides a strong prognostic signal which could be valuable for specific patients; and d) gastric tonometry has been clearly validated and is still been widely used in the experimental setting, providing a strong physiologic signal that probably deserves to be further explored in the clinical arena.

Conclusions

Our study failed to demonstrate any survival benefit of using pHi compared to cardiac index as resuscitation goal in septic shock patients. Nevertheless, a normalization of pHi within 24 hours of resuscitation is a strong signal of therapeutic success and in contrast, a persistent low pHi despite treatment is associated with a very bad prognosis in septic shock patients. Future studies should evaluate a potential adjunctant role of tonometric guided resuscitation at earlier stages of septic shock.

Key messages

- A resuscitation strategy aimed at normalizing pHi offers no survival advantage compared to cardiac index guided resuscitation in septic shock patients.
- A normalization of pHi within 24 hours of resuscitation is a strong signal of therapeutic success during septic shock resuscitation.
- A persistent low pHi despite treatment is associated with a very bad prognosis in septic shock patients.

Abbreviations

pHi: Gastric intramucosal pH

CI: Cardiac index

TISS: Therapeutic Intervention Scoring System

EGDT: Early Goal Directed Therapy

ScvO2: Central venous oxygen saturation

SmvO2: Mixed venous oxygen saturation

ATS: American Thoracic Society

ACCP: America College of Chest Physicians

SCCM: Society of Critical Care Medicine

PAC: Pulmonary artery catheter

pCO2: Partial pressure of carbon dioxide

SS: Steady state

APACHE II: Acute Physiologic and Chronic Health Evaluation score

SOFA: Sepsis-related Organ Failure Assessment

ROC: Receiver operator characteristic curve

Competing interests

The authors declare that they have no competing interests.

Authors' Contributions

FP conceived the study, and participated in its design and coordination and helped to draft the manuscript. AD conceived the study, and participated in its design and coordination and helped to draft the manuscript. EK participated in its coordination. TR helped to draft the manuscript and performed the statistical analysis. AB recruited patients and helped to draft the manuscript. NB participated in its coordination and recruited patients. SL participated in its coordination and recruited patients. GH conceived the study, and participated in its design and coordination and helped to draft the manuscript. All authors read and approved the final manuscript.

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Figure legends

Figure 1

Septic shock resuscitation protocol

Figure 2

Kaplan–Meier survival curves for both groups.

Figure 3

Receiver operator characteristic (ROC) curves for mortality for both groups at admission, 24 and 48 hours.

Table 1. Demographic and clinical data at baseline.

	CI Group (n = 66)	pHi Group (n = 64)	*p-value*
Age (yrs.)	57.4 ± 15.9	59.9 ± 15.9	0.38
Gender (male/female)	42/24	33/31	0.2
Admission APACHE II	18.5 ± 3,8	19.4 ± 5.6	0.3
Admission SOFA	8.8 ± 2,7	10.6 ± 3.6	< 0.05*
Sepsis source			
Abdominal n/(%)	43 (65)	45 (70)	
Pneumonia n/(%)	15 (23)	11 (17)	
Urinary n/(%)	4 (6)	6 (9)	
Others n/(%)	4 (6)	2 (3)	

CI: Cardiac Index; SOFA: Sequential organ failure assessment score.

(*) $p<0.05$ considered as significant. Unpaired t test and chi-square test for p values.

Table 2. Comparison of target values between survivors and non-survivors in both groups at different time points.

	Admission (n)	24 Hours (n)	48 Hours (n)
CI group *Cardiac Index*			
Total (66)	4.3 ± 1.1	4.05 ± 0.9	3.57± 1.3
Survivors (46)	4.46 ± 1.02 (46)	4.18 ± 0.7 (44)	3.56 ± 1.5 (24)
Non survivors (20)	3.94 ± 1.20 (20)	3.78 ± 1.0 (20)	3.58 ± 0.9 (16)
*p**	*NS*	*NS*	*NS*
pHi group *pHi*			
Total (64)	7.3 ± 0.12	7.3 ± 0.1	7.28 ± 0.12
Survivors (46)	7.32 ± 0.12 (46)	7.36 ± 0.06 (46)	7.33 ± 0.10 (20)
Non survivors (18)	7.26 ± 0.12 (18)	7.19 ± 0.10 (18)	7.20 ± 0.13 (14)
*p***	*NS*	*<0.001*	*<0.003*
Cardiac Index			
Total (64)	3.8 ± 1.1	3.8 ± 1.1	4.04 ± 1.5
Survivors (46)	3.66 ± 0.9 (46)	3.83 ± 1.1 (46)	3.47 ± 0.80 (20)
Non survivors (18)	4.23 ± 1.4 (18)	3.93 ± 1.2 (18)	4.27 ± 1.29 (14)
*p****	*NS*	*NS*	*NS*

*CI of survivors vs. non-survivors in the CI group;

**pHi of survivors vs. non-survivors in the pHi group;

***CI of survivors vs. non-survivors in the pHi group.

$p<0.05$ considered as significant. Unpaired t-test for p values.

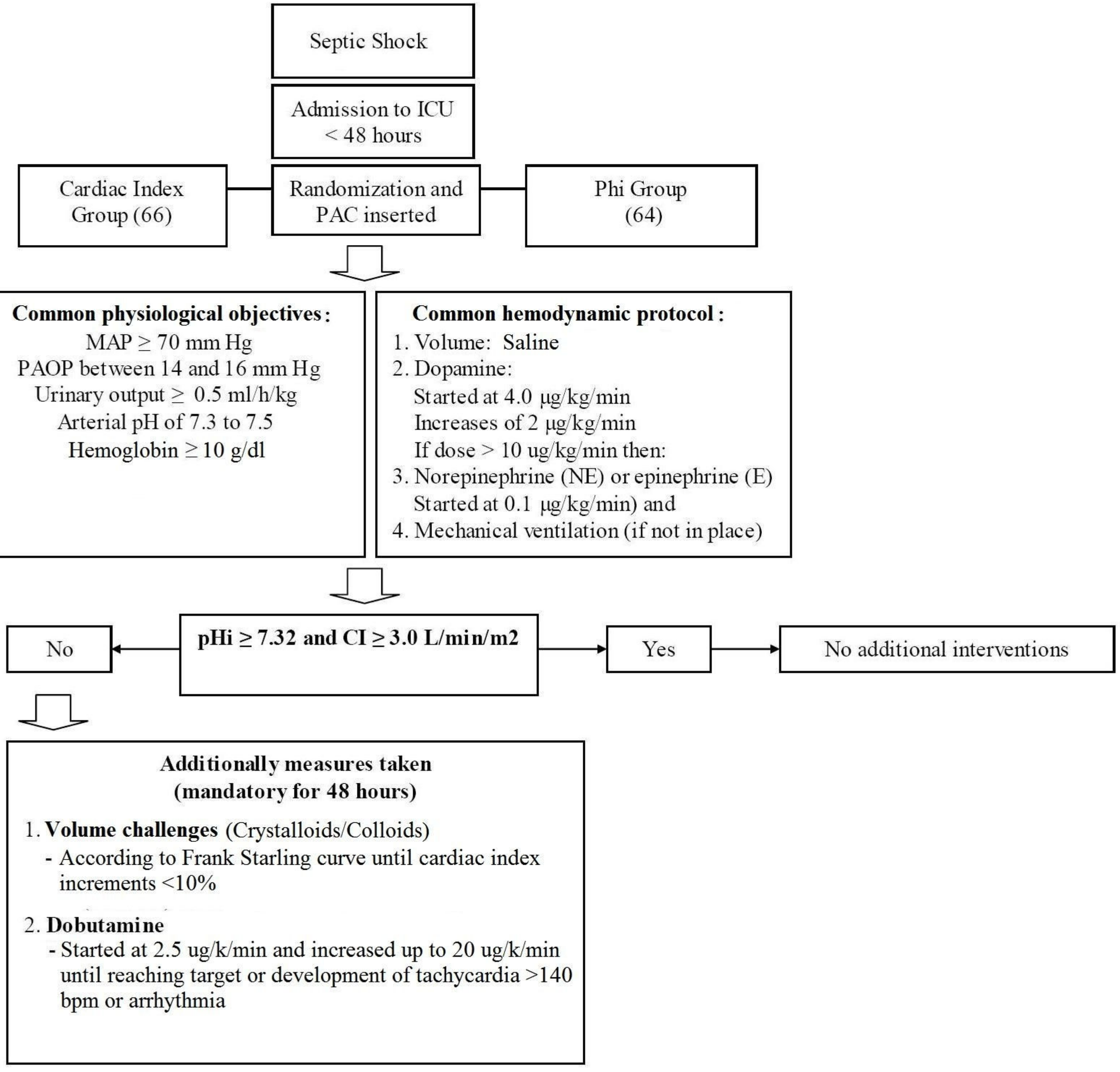

Septic Shock
Admission to ICU
< 48 hours
Cardiac Index
Group (66)
Randomization and
PAC inserted
Phi Group
(64)
Common physiological objectives:
MAP ≥ 70 mm Hg
PAOP between 14 and 16 mm Hg
Urinary output ≥ 0.5 ml/h/kg
Arterial pH of 7.3 to 7.5
Hemoglobin ≥ 10 g/dl
Common hemodynamic protocol:
1. Volume: Saline
2. Dopamine:
Started at 4.0 μg/kg/min
Increases of 2 μg/kg/min
If dose > 10 ug/kg/min then:
3. Norepinephrine (NE) or epinephrine (E)
Started at 0.1 μg/kg/min) and
4. Mechanical ventilation (if not in place)
pHi ≥ 7.32 and CI ≥ 3.0 L/min/m2
No
Yes
No additional interventions
Additionally measures taken
(mandatory for 48 hours)
1. Volume challenges (Crystalloids/Colloids)
- According to Frank Starling curve until cardiac index increments <10%
2. Dobutamine
- Started at 2.5 ug/k/min and increased up to 20 ug/k/min until reaching target or development of tachycardia >140 bpm or arrhythmia

Figure 1

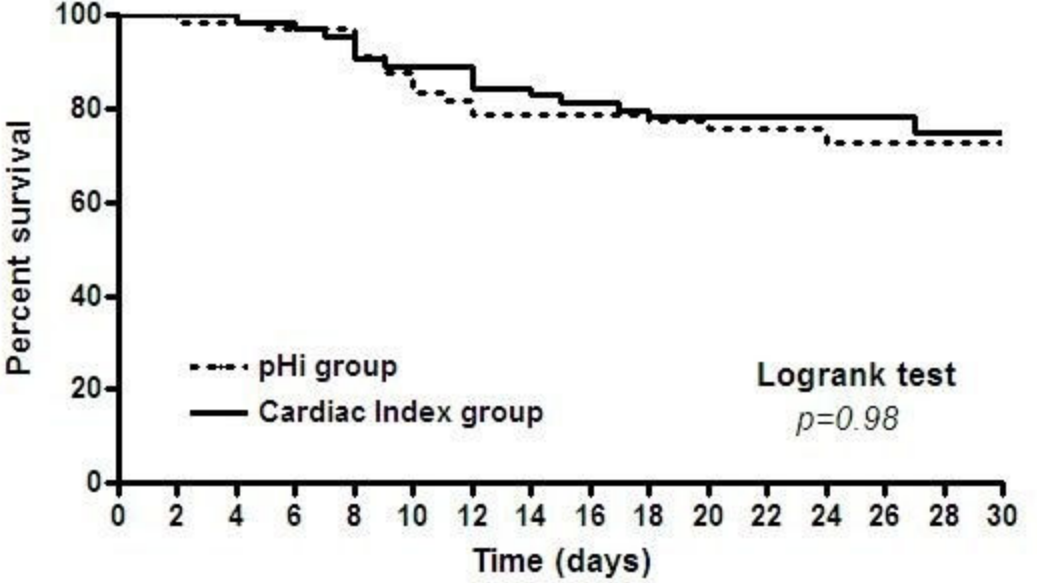
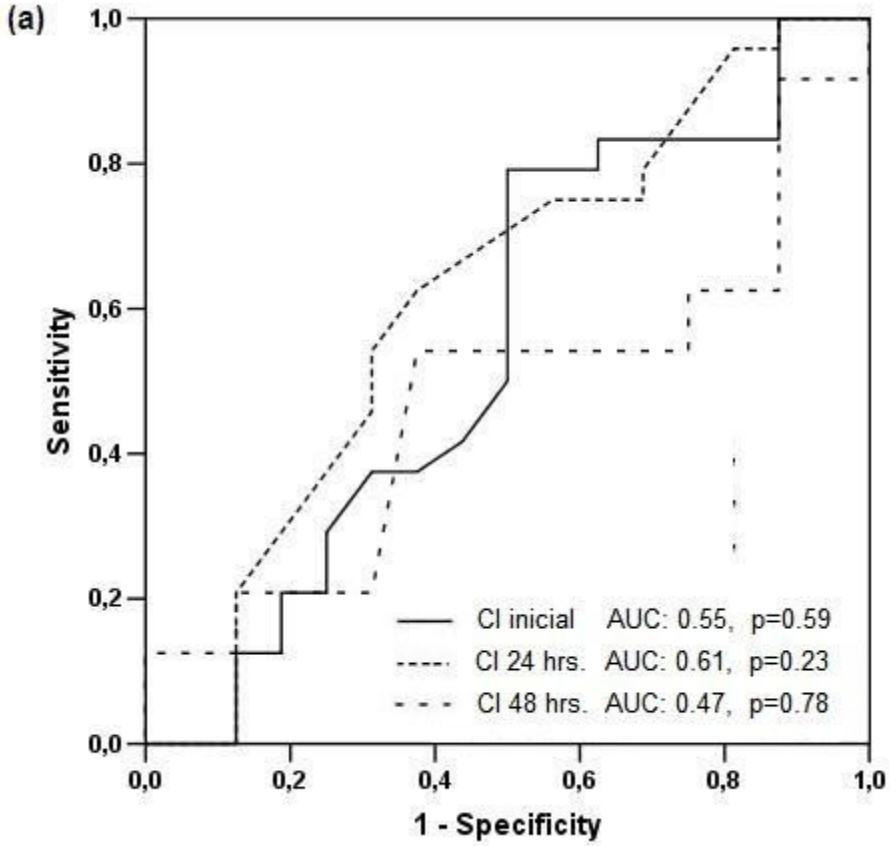

100
80
60
40
20
0
Percent survival
pHi group
Cardiac Index group
Logrank test
p=0.98
0
2
4
6
8
10
12
14
16
18
20
22
24
26
28
30
Time (days)

Figure 2


(a)
Sensitivity
1 - Specificity
0,0
0,2
0,4
0,6
0,8
1,0
Cl inicial AUC: 0.55, p=0.59
Cl 24 hrs. AUC: 0.61, p=0.23
Cl 48 hrs. AUC: 0.47, p=0.78

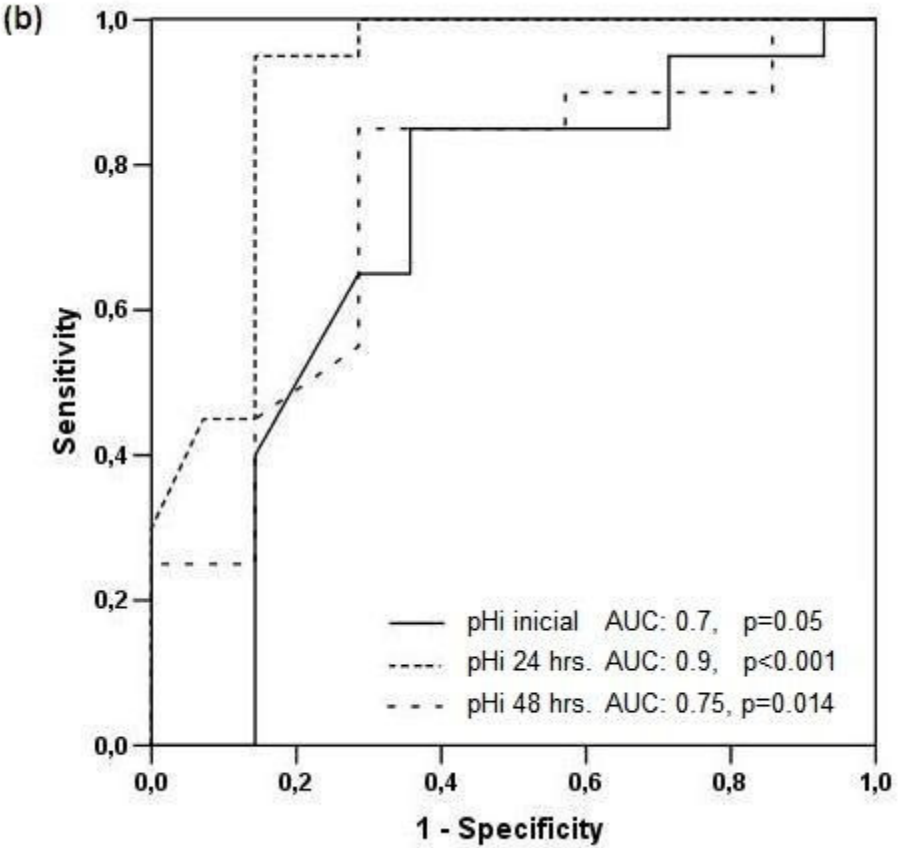

(b)
Sensitivity
1 - Specificity
0,0
0,2
0,4
0,6
0,8
1,0
pHi inicial AUC: 0.7, p=0.05
pHi 24 hrs. AUC: 0.9, p<0.001
pHi 48 hrs. AUC: 0.75, p=0.014

Figure 3