

ORIGINAL

ECAIS study: Inadvertent cardiovascular adverse events in sepsis[☆]

M. Gomez Duque^a, C. Enciso Olivera^b, E. Peña Torres^c, O.D. Segura Durán^d,
V.H. Nieto Estrada^{e,*}

^a Comité de Ética en Investigación, CEISH, Hospital Universitario de San José, Bogotá, Colombia

^b Unidad de Cuidados Intensivos, Hospital Universitario Infantil de San José, Bogotá, Colombia

^c División en Investigaciones, Fundación Universitaria de Ciencias de la Salud, Bogotá, Colombia

^d Fundación Universitaria de Ciencias de la Salud, Bogotá, Colombia

^e Unidad de Medicina Crítica y Cuidados Intensivos, Hospital Universitario de San José, Bogotá, Colombia

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KEYWORDS

Myocardial ischemia;
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Abstract

Objective: To describe the incidence of cardiovascular adverse events in patients with sepsis in its various stages.

Design: A longitudinal, descriptive, observational study was carried out.

Setting: Intensive care units (ICUs) of two university hospitals in Bogotá (Colombia).

Patients: A number of patients consecutively admitted to the adult ICU with a diagnosis of sepsis, and no evidence of previous ischemic myocardial injury.

Interventions: Forty-eight hours of electrocardiographic record using Holter technology.

Main variables: Ischemia, cardiac arrhythmia, heart rate variability (HRV).

Results: A total of 100 patients were analyzed, 62% being staged as presenting septic shock. Three percent suffered ischemic events detected by Holter and unnoticed through conventional monitoring. Forty-six percent suffered an arrhythmic event detected by Holter, compared with only 6% as detected by conventional monitoring. Mortality was 40%. All patients showed loss of HRV.

Conclusion: In this study patients with sepsis showed a low incidence of cardiovascular ischemic events. In contrast, arrhythmic events showed a high incidence. Conventional monitoring failed to detect any of the ischemic events and most arrhythmic events. In this study, cardiovascular events generated by adrenergic discharge had no impact upon mortality.

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* Corresponding author.

E-mail address: victorhugonieto@aol.com (V.H. Nieto Estrada).

PALABRAS CLAVE

Isquemia miocárdica;
Electrocardiografía
ambulatoria;
Sepsis;
Choque séptico

Estudio ECAIS: eventos cardiovasculares adversos inadvertidos en sepsis**Resumen**

Objetivo: Describir la incidencia de eventos cardiovasculares adversos en pacientes con diagnóstico de sepsis en sus diferentes estadios.

Diseño: Estudio observacional, descriptivo, longitudinal.

Ámbito: Unidades de cuidados intensivos de tipo mixto de dos hospitales universitarios en la ciudad de Bogotá.

Participantes: Se incluyeron una serie de pacientes mayores de edad, que ingresan a UCI con diagnóstico de sepsis, sin evidencia de lesión miocárdica isquémica previa.

Intervenciones: Registros electrocardiográficos continuos de 12 derivaciones durante 48 horas con monitoría Holter.

Variables de interés: Isquemia, arritmia cardiaca, variabilidad de la frecuencia cardiaca.

Resultados: Se analizaron 100 pacientes, 62% de los cuales se estadió como choque séptico. El 3% presentó evento cardiovascular adverso de tipo isquémico detectado por Holter y desapercibido por monitoreo convencional. El 46% presentaron un evento de tipo arritmico por Holter, comparado con solo un 6% detectado por monitoreo convencional. La mortalidad cruda fue de 40%. El 100% presentó pérdida de la variabilidad de la frecuencia cardiaca.

Conclusión: La sepsis en esta experiencia mostró una baja incidencia de eventos cardiovasculares isquémicos. Los eventos arritmicos, sin embargo, mostraron una incidencia alta. El monitoreo convencional falló en detectar la totalidad de los eventos isquémicos y en mayor proporción los eventos arritmicos. En esta serie, los eventos cardiovasculares generados por descarga adrenérgica no impactan en la mortalidad.

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Introduction

The incidence of sepsis has increased in recent years due to different factors.¹ It is the main cause of death in non-coronary critical patients, with a mortality rate of between 19.6% and 59%.^{2,3} Mortality in such cases is attributable to failure of different organs, including particularly the cardiovascular system.⁴

The pathogenesis of myocardial dysfunction due to sepsis is of a multifactorial nature, and includes ischemia.^{5,6} In this context, an increase in coronary flow is described, though some areas suffer oxygen deficiency—resulting in a phenomenon similar to that of myocardial hibernation.⁷ Alterations in capillary flow and in coagulation homeostasis are considered to be the bases of this process.^{8,9} Thus, myocardial dysfunction cannot be attributed to generalized myocardial ischemia.^{10,11} Other elements alter ventricular function in sepsis, including interleukins,¹² tumor necrosis factor, and a specific circulating humoral factor probably of pancreatic origin.¹³

The initial clinical picture is characterized by a loss of vascular tone, a hyperdynamic phase with increased cardiac output, and subsequently myocardial depression with contractility alterations,¹⁴ relaxation disorders, tachycardia¹⁵ and dilatation of the heart cavities.¹⁶ There is no typical arrhythmogenic profile, though the systemic inflammatory response—independently of its etiology—is intrinsically arrhythmogenic.¹⁷ Alterations are observed in the equilibrium of the autonomous control of heart function, resulting in incompetent chronotropism that reduces HRV.¹⁸

Parasympathetic control is attributed with an antiinflammatory effect mediated by attenuation of the production of splanchnic tumor necrosis factor-alpha.¹⁸

Finally, the elevated heart rate increases myocardial stress and oxygen demand.¹⁹

In clinical practice, cardiovascular monitoring is the basis for the making of many decisions.²⁰ To date, however, there are no technical elements that meet all the criteria of an ideal monitoring system.²¹ In the specific case of myocardial ischemia, basic monitorization does not meet the operative requirements for diagnosing an acute event.²²

Considering a high probability of inadvertent myocardial ischemia in the septic patient, we contemplate close electrocardiographic monitorization of these patients.

Materials and methods

A longitudinal, descriptive observational study was designed, with information collected from 48-h Holter monitoring as the primary data source.

Study population and sample

The study covered the period between July 2009 and October 2010, and included patients over 18 years of age with a diagnosis of sepsis and admitted to the ICU within the first 24 h of symptoms onset, with the need for cardiovascular or ventilatory support. Exclusion criteria were clinical or electrocardiographic features complicating interpretation of the Holter recordings, and patients with coronary disease.

Table 1 Statistical parameters for assessing cardiovascular risk.

| | | |
|-------|---|--|
| SDNN | Standard deviation of the intervals RR or NN (normal) | <50 = high risk 50–100 = moderate risk >100 = low risk |
| PNN50 | Percentage of intervals differing by more than 50 ms with respect to the preceding interval | <3% = high risk ≥3% = low risk |

The Holter recordings were made using a Cardioex MMC10L system with three electrocardiography channels. Recording was started in the first 6 h of admission and was continued until completing 48 h. The interpretation of the tracings was made by one of two cardiologists based on randomized assignment and following the current consensus parameters.^{23,24}

Cardiovascular adverse events secondary to myocardial ischemia were regarded as arrhythmias and loss of variability of the heart rate. The detection of ischemia was based on ST-segment analysis.

For the evaluation of HRV, use was made of the statistical indices standard deviation of the RR intervals (SDNN) and percentage of intervals differing by more than 50 ms from the preceding interval (PNN50), in relation to sympathetic and parasympathetic activity, respectively.^{25,26}

These indices have been used for the prediction of mortality risk after infarction; SDNN < 50 ms and PNN50 < 3% identify those patients with severely reduced HRV²⁶ (Table 1).

Conventional cardiac monitorization was carried out with the visioscope, obtaining registries of one to two channels.

Statistical analysis

The STATA SE version 10.1 package was used for the statistical analysis. A descriptive study of the data was made based on absolute frequencies and percentages in the case of categorical variables, and central tendency and dispersion measures in the case of quantitative variables. Multiple correspondence analysis was performed with SPAD 7.0. The illustrating variable was sepsis stage, while the cardiovascular adverse events represented the active variables.

Ethical issues

The study was approved by the Ethics Committees of the participating institutions, being regarded as entailing only minimum risk according to current legislation.²⁷ Informed consent was obtained from all patients.

Results

A total of 130 eligible adults were admitted between July 2009 and October 2010 with a diagnosis of sepsis and requiring cardiovascular and/or ventilatory support, and who met the screening criteria. Thirty subjects were excluded due to poor data quality.

The general population and the patients grouped by sepsis stage were characterized.

Ten percent of the patients were admitted with a diagnosis of sepsis, 28% with a diagnosis of severe sepsis, and 62% with septic shock—the latter category being defined not only by the use of vasopressor drugs but also by the presence of clinical manifestations of tissue hypoperfusion. The global median age was 55 ± 26 years (range 18–88 years). The male:female ratio was 1.38:1.

In the general population, admission due to clinical causes was slightly predominant (53%). This tendency was also seen in the groups of patients with sepsis and severe sepsis, though surgical patients were seen to predominate in the septic shock group (56.5%). Regarding the cardiovascular risk factors, arterial hypertension predominated (33%), followed by patient age over 65 years (24%), obesity (18%) and diabetes mellitus (12%).

The median APACHE severity score was 16.5 ± 10 among the global patients, versus 18 ± 9 in those with septic shock.

Globally, the most frequent septic focus was the lungs (38%), while abdominal cavity infections were seen to predominate in the septic shock group (41.9%) (Table 2).

A total of 72% of the patients required vasopressor drugs, 7% were prescribed inotropic agents, and 45% required monitorization of cardiac output. This was done using Vigileo® technology; the recorded hemodynamic profile indicated a mean systolic volume index (SVI) of 32 ml/beat and a mean systolic volume variability (SVV) of 10%.

Conventional monitorization detected no ischemic event, while arrhythmias were identified in 6%. Holter analysis determined the presence of ischemia in three patients (Table 3).

Arrhythmic events were detected by Holter recording in 46% of the population, their origin being classified as follows: monomorphic ventricular tachycardia (21%), idioventricular rhythm (3%), atrial tachycardia (30%) and atrial fibrillation (5%). A higher frequency of arrhythmias was observed in the patients with septic shock and in patients with an increased loss of HRV (Table 4).

The global mortality rate was 40%. One of the three patients with a diagnosis of ischemia died, while in the patients with arrhythmic events the mortality rate was 40.1%.

The loss of HRV was less pronounced in the sepsis category, with median values for SDNN and PNN50 of 81.5 ms and 1.5%, respectively, versus 68 ms and 0% in the septic shock category (Table 5).

In the patients administered vasopressor drugs, the median SDNN was 68 ± 46.5, versus 61 ± 87 in those

Table 2 Epidemiological characteristics of the studied patients.

| Characteristics | Sepsis 10 (10%) | Severe sepsis 28 (28%) | Septic shock 62 (62%) | General 100 (100%) |
|---|--------------------|---------------------------|--------------------------|-----------------------|
| <i>Median age ± IQR^a [minimum, maximum]</i> | 50 ± 31 [32.81] | 54 ± 29.5 [20.85] | 56 ± 23 [18.88] | 55 ± 26 [18.88] |
| <i>Gender, n (%)</i> | | | | |
| Female | 2 (20) | 16 (57.1) | 40 (64.5) | 58 (58) |
| Male | 8 (80) | 12 (42.9) | 22 (35.5) | 42 (42) |
| <i>Admission, n (%)</i> | | | | |
| Clinical | 7 (70) | 19 (67.9) | 27 (43.5) | 53 (53) |
| Surgical | 3 (30) | 9 (32.1) | 35 (56.5) | 48 (48) |
| <i>Risk factors, n (%)</i> | | | | |
| Hypertension | 1 (10) | 10 (35.7) | 22 (35.5) | 33 (33) |
| Obesity | 1 (10) | 4 (14.3) | 13 (21) | 18 (18) |
| Age > 65 years | 1 (10) | 8 (28.6) | 15 (24.2) | 24 (24) |
| Diabetes | 1 (10) | 2 (7.1) | 9 (14.5) | 12 (12) |
| Hypothyroidism | 0 (0) | 0 (0) | 7 (11.3) | 7 (7) |
| Dyslipidemia | 0 (0) | 1 (3.6) | 5 (8.06) | 6 (6) |
| <i>APACHE median ± IQR^a [minimum, maximum]</i> | 15.5 ± 13 [6.29] | 14.5 ± 11.5 [6.30] | 18 ± 9 [6.30] | 16.5 ± 10 [6.30] |
| <i>Focus, n (%)</i> | | | | |
| Lung | 4 (40) | 13 (46.4) | 21 (33.9) | 38 (38) |
| Abdomen | 2 (20) | 6 (21.4) | 26 (41.9) | 34 (34) |
| Urinary | 1 (10) | 2 (7.1) | 3 (4.8) | 6 (6) |
| Bacteremia | 0 (0) | 1 (3.6) | 2 (3.2) | 3 (3) |
| Soft tissues | 0 (0) | 2 (7.1) | 0 (0) | 2 (2) |
| Others | 3 (30) | 4 (14.3) | 10 (16.1) | 17 (17) |
| <i>Monitorization</i> | 1 (10) | 5 (17.9) | 39 (62.9) | 45 (45) |
| <i>Inotropic agents</i> | 0 (0) | 0 (0) | 7 (11.3) | 7 (7) |
| <i>Vasopressors</i> | 4 (40) | 7 (25) | 61 (98.4) | 72 (72) |
| <i>Arrhythmic event, n (%)</i> | 4 (40) | 11 (39.3) | 31 (50) | 46 (46) |
| <i>Ischemic event, n (%)</i> | 0 (0) | 2 (7.1) | 1 (1.6) | 3 (3) |
| <i>Mortality</i> | 1 (10) | 9 (32.1) | 30 (48.4) | 40 (40) |

^a Inter-quartile range.

administered inotropic agents. In turn, the median SDNN in the patients administered with neither vasopressors nor inotropic agents was greater.

Among the survivors, the median SDNN was 72.5 ± 42 , compared with 61 ± 45 among those who died.

Application was made to this population of the mortality risk categorization used in coronary patients—a PNN50 proportion of 76% being found in the high risk category, where the mortality rate was 44.7%. In turn, according to SDNN, 78% of the population corresponded to the moderate and high risk groups, with a 51.9% mortality rate in the latter group (Table 6).

In the multiple correspondence analysis, and taking as illustrating variable the sepsis stage, with arrhythmic events, HRV, mortality and vasoactive drug use as active variables, septic shock was seen to be related to an increased HRV, more arrhythmias and greater mortality. Ischemic events were not related to sepsis stage (Fig. 1).

Discussion

An evaluation was made of the incidence of ischemic events based on 4800 h of Holter monitorization. The findings were

Table 3 Cardiovascular adverse events.

| | General | Arrhythmia | Ischemia |
|---|-----------|------------|----------|
| Detection by conventional monitorization, n (%) | | 6 (6) | 0 (0) |
| Detection by Holter | | 46 (100) | 3 (100) |
| Mortality, n (%) | 40 (40) | 18 (40.1) | 1 (33) |
| Days of stay Me ^a [range] | 10 [1–71] | 9.5 [1–47] | 18 [8–6] |

^a Median.

Table 4 Description of arrhythmic events.

| | Non-sustained monomorphic ventricular tachycardia n (%) | Idioventricular rhythm n (%) | Self-limiting atrial tachycardia n (%) | Atrial fibrillation n (%) |
|------------------------------------|--|---------------------------------|---|------------------------------|
| <i>Sepsis stage</i> | 21 (21) | 3 (3) | 30 (30) | 5 (5) |
| Sepsis | 1 (4.8) | 0 (0) | 4 (13.3) | 0 (0) |
| Severe sepsis | 5 (23.8) | 0 (0) | 7 (23.3) | 1 (20) |
| Septic shock | 15 (71.4) | 3 (100) | 19 (63.4) | 4 (80) |
| <i>PNN50</i> | | | | |
| High | 15 (71.4) | 2 (66.7) | 22 (73.3) | 4 (80) |
| Low | 6 (27.3) | 1 (33.3) | 8 (26.7) | 1 (20) |
| <i>SDNN</i> | | | | |
| High | 5 (23.8) | 0 (0) | 10 (33.3) | 2 (40) |
| Moderate | 11 (52.4) | 2 (66.7) | 11 (36.7) | 2 (40) |
| Low | 5 (23.8) | 1 (33.3) | 9 (30) | 1 (20) |
| <i>Conventional monitorization</i> | 2 (9.5) | 0 (0) | 3 (10) | 1 (20) |
| <i>Inotropic agents</i> | 0 (0) | 1 (33.3) | 1 (3.33) | 0 (0) |
| <i>Vasopressors</i> | 16 (76.2) | 3 (100) | 22 (73.3) | 5 (100) |
| <i>Mortality</i> | 7 (33.3) | 2 (66.7) | 13 (43.3) | 1 (20) |

Table 5 Heart rate variability indices.

| | SDNN | | | | PNN50 | | | |
|-------------------------|--------|------|---------|---------|--------|-----|---------|---------|
| | Median | IQR | Minimum | Maximum | Median | IQR | Minimum | Maximum |
| Sepsis | 93 | 47 | 14 | 221 | 0 | 2 | 0 | 30 |
| Severe sepsis | 81.5 | 38 | 16 | 161 | 1.5 | 6 | 0 | 7 |
| Septic shock | 62 | 47.5 | 14 | 161 | 0 | 1.5 | 0 | 7 |
| With vasopressors | 68 | 45 | 24 | 221 | 0 | 3 | 0 | 30 |
| Without vasopressors | 68 | 46.5 | 17 | 221 | 0 | 2 | 0 | 71 |
| With inotropic drugs | 73 | 45 | 14 | 163 | 0 | 3.5 | 0 | 9 |
| Without inotropic drugs | 61 | 87 | 33 | 163 | 0 | 3 | 0 | 9 |
| Alive | 68 | 45 | 14 | 221 | 0 | 2 | 0 | 71 |
| Deceased | 72.5 | 42 | 17 | 219 | 1 | 4 | 0 | 30 |
| | 61 | 45 | 14 | 221 | 0 | 1 | 0 | 9 |

Table 6 Classification of cardiovascular risk according to heart rate variability indices.

| | Alive n (%) | Deceased n (%) | General n (%) |
|--------------|----------------|-------------------|------------------|
| <i>PNN50</i> | | | |
| High | 42 (55.3) | 34 (44.7) | 76 (76) |
| Low | 18 (75) | 6 (25) | 24 (24) |
| <i>SDNN</i> | | | |
| High | 13 (48.1) | 14 (51.9) | 27 (27) |
| Moderate | 33 (64.7) | 18 (35.3) | 51 (51) |
| Low | 14 (63.6) | 8 (36.4) | 22 (22) |

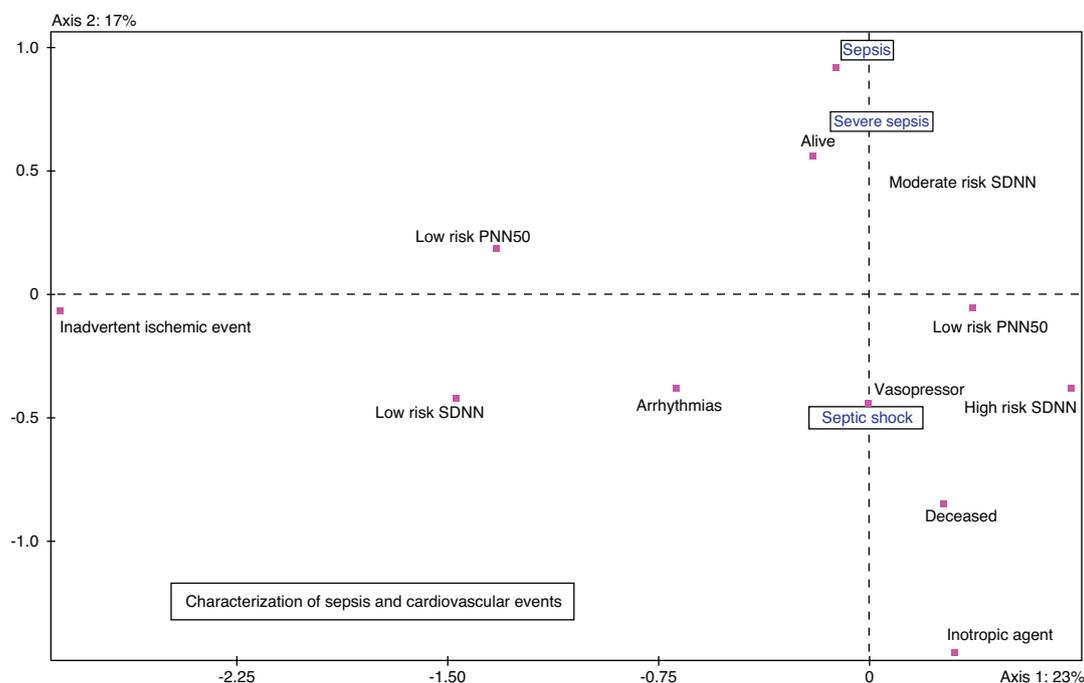


Figure 1 Sepsis and cardiovascular events characterization factorial plot.

scantly significant, and ischemia does not appear to be the primary cardiovascular event induced by sepsis.²⁸

Activation of the systemic inflammatory response is the cause of the main manifestations of sepsis.^{29,30} The available evidence suggests that uncontrolled inflammation can trigger myocardial ischemia in previously diseased coronary vessels,^{31–33} and can depress ventricular function from the start of sepsis.³⁴

In the present study ischemia was not shown to be the main physiopathological event related to ventricular dysfunction, though the presence of arrhythmias and the loss of HRV were seen to be important elements in that they constituted inadvertent cardiovascular events related to the imbalance between sympathetic and parasympathetic activity.³⁵

An inconvenience of this study is its descriptive nature, given the scant theoretical basis upon which to support an analytical study.

The patients who suffered ischemic events were not detected by conventional monitorization, and the diagnosis was established by Holter monitorization. The events were transient, and none of them required stratification to invasive management.

This low incidence of ischemic events coincides with the observations of Cunnion and Schaer,¹⁰ who described normal or increased coronary flow in four of 7 septic patients with myocardial depression, and with the data published by Dhainaut and Huyghebaert, who identified myocardial ischemia in 6 of 40 septic patients on the basis of myocardial lactate production—though they also underscored that lactate is a poor indicator of myocardial ischemia.¹¹

Arrhythmias were present in close to 50% of the patients, with a larger number of cases in the shock staging groups—almost all being diagnosed during Holter

monitorization and characterized as atrial tachycardia, atrial fibrillation, ventricular tachycardia and idioventricular rhythm. None of these events was of a sustained nature.

HRV reflects the equilibrium of autonomous nervous system control of heart function,¹⁸ and has been reported to offer many applications.²⁶ Sepsis has been found to involve a loss of HRV—this in turn being related to negative patient outcomes.³⁶

This is the first series involving 100 patients to demonstrate a loss of HRV, as evaluated by the statistical indices SDNN and PNN50, which are associated to sympathetic hyperactivity and to a loss of parasympathetic control, respectively—this phenomenon being observed in septic cardiomyopathy.³⁵

No validation has been made of the use of the post-infarction risk stratification scale with HRV in septic patients. It was applied with the aim of grouping the data referred to these indices in the population. In this context, an increased distribution in the high risk categories was observed.

The higher median values of SDNN and PNN50 in the sepsis category suggest a lesser loss of HRV. The deceased patients showed a greater loss of variability—this finding coinciding with the observations of Chen and Kuo,³⁷ who demonstrated the predictive capacity of HRV in relation to in-hospital mortality among patients with sepsis.³⁷

The use of inotropic agents and vasopressors was concordant with the current resuscitation protocols,³⁸ and the patients who received such therapy showed a greater loss of HRV. The utilization of inotropic agents was low, even while acknowledging that advanced stage septic cardiomyopathy is a myocardial depression state. With this consideration in mind, an analysis was made of the hemodynamic profile of 26 patients subjected to cardiac output monitorization in parallel to Holter recording. The technique used was based on

analysis of the pulse wave profile, using the Vigileo® system. We accumulated 100h of monitorization, with mean values for SVI and SVV of 32 and 10, respectively, which is consistent with myocardial depression, as described and confirmed by Parrillo.³⁹

In our group of patients, cardiovascular behavior related to sepsis was no different from that found in previous descriptions, discarding the possibility that myocardial ischemia is significant in septic myocardial depression factors.

On the other hand, the incidence of arrhythmic events and the loss of HRV deserve close attention—representing the true inadvertent cardiovascular events in sepsis, and opening a new field of research for establishing the potential benefits of different treatments, with a view to modifying sympathetic activity. New studies with control groups are needed to compare the phenomenon of HRV which we have found in septic patients versus other disease conditions commonly observed in the ICU.

Improvements are required in continuous monitorization techniques, with the consideration of modifications in conventional electrocardiography or more closer monitoring of contractility in patients at risk, giving the limitations of conventional cardiac monitorization in diagnosing cardiovascular events in septic patients.

Conflicts of interest

The authors declare no conflicts of interest.

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