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Autonomic control of the heart
and peripheral vessels
in human septic shock

Abstract  Objective: Circulating endotoxin impairs the sympathetic
regulation of the cardiovascular system in animals. We studied the
changes in the autonomic control of the heart and circulation during
septic shock in humans.
Design: 12 patients (age 43.0±6,
17–83 years) were investigated dur-
ing septic shock (mean duration:
3.5±0.5 days) and during recovery,
fluctuations in R-R interval, inva-
sive arterial pressure (AP) and pe-
ripheral arteriolar circulation (PC,
photoplethysmography) were evalu-
ated by spectral analysis as a vali-
dated noninvasive measure of sym-
pathovagal tone. Apache II score
was adopted as the disease severity
index. Low frequency components
(0.03–0.15 Hz) of the frequency
spectra were expressed as relative to
the overall variability (LFnu) for
each cardiovascular variable.
Results: LFnu were low or absent
during shock but, in the 10 patients
who recovered, increased by the
time of discharge (post-shock). R-R
LFnu increased from 17±6 to
47±9 (p<0.03), AP LFnu from
6±3 to 35±4 (p<0.02) and PC
LFnu from 18±3 to 66±4
(p<0.001). Apache II fell from
23.1±1, at admission, to 14.8±1.8
at discharge (p<0.005). Two pa-
tients died showing no LFnu in-
crease.
Conclusion: Reduced LF compo-
nents of the variability of cardio-
vascular signals are characteristic of
septic shock, confirming the pres-
ence of abnormal autonomic control.
Restored sympathetic (LF) modula-
tion seems to be associated
with a favourable prognosis.

Key words  Autonomic nervous
system  Sepsis syndrome
Peripheral circulation  Heart rate
variability  Blood pressure
variability  Spectral analysis
Adrenergic receptors  Intensive
care

Introduction

Septic shock has been recognised with increasing frequen-
cy in the last 15 years [1] and is considered as the com-
monest single cause of late death in Intensive Therapy
Units [2]. Major life-threatening pathophysiology relates
to the cardiovascular system which consequently should
result in activation of the sympathetic nervous system. In-
deed some animal models have shown that the sympa-
thetic nervous system is activated as a defence response to
systemic sepsis. Cumming et al. [3] observed increased ar-
terial plasma catecholamine and renin activity in response
to bacterial peritonitis in sheep. However, inoculation of
rabbits with endotoxin has been shown to reduce renal
sympathetic activity as characterised by the renal nerve
discharge and has been associated with a reduction in
mean arterial pressure [4]. In humans, affection of the
nervous system during septic shock is manifested clinically as septic encephalopathy and peripheral polyneuropathy [5].

There is evidence of myocardial dysfunction in septic shock [6], which has been attributed to a circulating myocardial depressant factor [7], or other mechanisms [8], including the down-regulation of sympathetic myocardial responsiveness [9, 10]. Information regarding autonomic regulation of the heart during the course of the septic shock syndrome in humans is scanty. A rapid increase in plasma levels of catecholamines reflecting increased sympathetic outflow is present in early phase of this syndrome [11], but a poor outcome is associated with reduced sensitivity towards β-receptor stimulation, indicating an impaired response to the sympathetic activation [12].

Defining a measure for the efferent neural traffic to the various components of the cardiovascular tree would possibly have important clinical and prognostic implications. To evaluate the changes in the autonomic control to the heart during the sepsis syndrome, we recently measured the neural traffic by spectral analysis of R-R interval variability. The total R-R interval variability and the sympathetically-mediated low frequency (LF) component were reduced suggesting an overall alteration in the autonomic control of the heart, involving mainly the sympathetic limb [13]. The sympathetic-parasympathetic balance can be assessed by autoregressive power spectral analysis of the beat to beat spontaneous fluctuations in several circulatory variables, other than R-R interval. The principles and the rationale of the method have been recently reviewed and has been shown to provide a convenient and noninvasive method for quantifying autonomic efferent activity of the cardiovascular system [14–16].

In view of the available animal and clinical studies of sepsis [3–5, 9–12], we hypothesised that impaired or down-regulated β-sympathetic responsiveness could be detected by power spectral analysis of other cardiovascular variables in critically ill patients with septic shock. In the present study, we therefore evaluated the changes in the autonomic control not only of the heart (R-R interval) but also of the circulation by spectral analysis of blood pressure and peripheral circulation using an autoregressive model.

Materials and methods

Subjects

The study was approved by the Central Oxford Research Ethics Committee. Twelve patients (7 males, 5 females, mean age 43.0±6, mean±SD, 17–83 years) were studied during consecutive days following admission to the Intensive Therapy Unit of the John Radcliffe Hospital (Oxford, UK) until discharge. None of the subjects studied had clinical evidence of pre-existing diabetes mellitus, chronic renal disease, neuropathy or autonomic disturbances, hypertension or cardiac disorders.

The presence of the septic shock was established on the basis of recognised clinical and physiological criteria [5, 17]. The sepsis criteria here considered are summarised in Table 1. Patient details, diagnoses, severity of illness and resolution of the disease are shown in Table 2. All patients during the period of sepsis (mean duration 3.5±0.5 days) were lying supine in bed and intubated; the mode of ventilation adopted was synchronised intermittent mandatory ventilation (SIMV) with the addition of 5–12 cmH2O continuous positive airway pressure (CPAP) to maintain adequate minute ventilation and gas exchange. During recovery, 10 remained intubated of which 4 patients were breathing spontaneously with pressure support. The PCO2 and PO2 were kept within physiological limits avoiding hyperventilation of the patients.

The patients received a range of sedative agents, analgesics and β-adrenergic agonists (Table 2). No subject was receiving any β-adrenergic blocking or cholinergic blocking agents. The level of sedation and analgesia were largely determined by clinical needs. Patients were maintained pain free with a level of sedation allowing response to medical and nursing staff.

Disease severity was assessed by the Apache II score which was derived from a combination of physiological variables combined with the Glasgow coma scale and a measure of previous chronic health status [18]. The scores were formulated on the basis of the patients data at the moment of signal acquisition.

Signal acquisition

With the patients resting in the supine position, the following signals were recorded:

i) R-R interval (R-R) was recorded in lead II by 3 adhesive ECG electrodes;

ii) respiration was obtained by impedance plethysmography (changes in chest wall impedance detected by the precordial electrodes). Impedance measures provided a volume amplitude signal proportional to the tidal volume which was then used to locate the respiratory component of the power spectra;

Table 1 Systemic sepsis: inclusion criteria

A. Evidence of a systemic response to infection

1. Clinical evidence of infection for, or a source of infection and
2. Rectal temperature >101° F (38.3° C) or <95° F (35.6° C)

Combined with:

B. Evidence of systemic organ dysfunction from two of the following:

3. Tachycardia (>90 beat/min) and tachypnoea (>20 breath/min)
4. Hypotension, systolic <90 mmHg, or 40 mHg drop in systolic
5. Unexplained acidosis pH <7.3
6. Hypoxaemia, P O2 <75 mmHg, 9 kPa (breathing room air) or P O2/FiO2 ratio <250 (mmHg) or <33 (kPa)
7. Oliguria (urine output <30 ml or 0.5 ml/kg for at least 1 h) despite adequate fluid loading
8. Unexplained elevated prothrombine time or partial thromboplastin time. Low platelets (<100000 or 50% drop)
9. Sudden unexplained alteration in the mental status
10. High cardiac index >4.1/min/m2, SVR <800 dyne·s/cm2