Research Paper

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Spectral analysis of heart rate variability in the sepsis syndrome

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SYMPATHETIC and parasympathetic activity was evaluated on 39 occasions in 17 patients with the sepsis syndrome, by measurement of the variation in resting heart rate using frequency spectrum analysis. Heart rate was recorded by electrocardiography and respiratory rate by impedance plethysmography. The sepsis syndrome was established on the basis of established clinical and physiological criteria. Subjects were studied, whenever possible, during the period of sepsis and during recovery. Spectral density of the beat-to-beat heart rate was measured within the low frequency band 0.04 to 0.10 Hz (low frequency power, LFP) modulated by sympathetic and parasympathetic activity, and within a 0.12 Hz band width at the respiratory frequency mode (respiratory frequency power, RFP) modulated by parasympathetic activity. Results were expressed as the total variability (total area beneath the power spectrum), as the spectral components normalized to the total power (LFP_n, RFP_n) or as the ratio of LFP/RFP. During the sepsis syndrome, total heart rate variability and the sympathetically mediated component, LFP_n were significantly lower than during the following recovery phase (ANOVA, $p < 0.0001$, $p < 0.01$ respectively). Both APACHE II (Acute Physiological and Chronic Health Evaluation) and TISS (Therapeutic Intervention Scoring System) scores showed an inverse correlation with total heart rate variability, logLFP, LFP_n and the LFP/RFP ratio ($p < 0.002$ to 0.0001). Sympathetically mediated heart rate variability was significantly lower during the sepsis syndrome and was inversely proportional to disease severity.

Key words: Sepsis syndrome, Intensive care, Heart rate variability, Spectral analysis, Respiration, Autonomic nervous system, Adrenergic receptors

Introduction

The sepsis syndrome is a major cause of multiple organ system failure and death complicating severe bacterial infection.[1,2] Despite the hyperdynamic state of the circulation there is often evidence of myocardial dysfunction[3,4] which has been attributed to a circulating myocardial depressant factor[5] or other mechanisms[6] including the down-regulation of sympathetic myocardial responsiveness.[7,8]

Reduced sympathetic responsiveness has also been demonstrated in patients with heart failure from other causes and following myocardial infarction by assessing the amount of heart rate variability.[9–14] Heart rate variability can be measured in several ways. However, spectral analysis of the beat-to-beat interval has proven to be a particularly convenient and reproducible method, not only of quantifying variability, but of characterizing the relative contributions of the sympathetic and parasympathetic nervous systems in animals,[15] healthy humans[16,17] and in several disease states.[9,18–23]

We therefore undertook a study of heart rate spectrum analysis in patients with the sepsis syndrome to evaluate heart rate variability and to assess the relative contributions of sympathetic and parasympathetic activity to that variability.

Materials and Methods

Subjects: Seventeen patients with sepsis syndrome, admitted to the John Radcliffe Hospital Intensive Therapy Unit were investigated. Details of the patients are shown in Table 1. All patients were studied while at rest and motionless in the supine position. None of the subjects studied had clinical evidence of pre-existing diabetes mellitus, chronic renal disease, hypertension or cardiac disorders.

The presence of the sepsis syndrome was established on the basis of recognized clinical and physiological criteria.[2] The precise sepsis criteria are summarized in Table 2. Measurements of heart rate variability were made during the period of clinical sepsis and repeated at a time when the patient was considered to have recovered and no longer to fulfil the sepsis criteria. The average, mean arterial blood pressure for the 17 patients during sepsis was 75 mmHg with eight patients having mean blood

Table 1. Details of the 17 patients studied

Subject (No.)	Age (years)	Gender (m/f)	Diagnosis
1	35	F	Urosepsis
2	23	M	Multiple trauma
3	45	M	Pancreatitis
4	21	M	Wegener's granuloma
5	63	F	Acute pancreatitis
6	83	F	Abdominal aortic aneurysm
7	52	F	Renal transplant/pneumonia
8	32	F	Multiple trauma
9	67	M	Colonic perforation
10	25	M	Ischaemic bowel
11	76	M	Acute pancreatitis
12	46	M	Acute endocarditis
13	29	F	Mediastinitis
14	73	M	Osteomyelitis
15	24	M	Multiple trauma
16	27	F	Peritonitis
17	57	F	Perforated duodenal ulcer
Mean	46	9M/8F	

Table 2. Clinical criteria for the presence of the sepsis syndrome

A. Evidence of a systemic response to infection
1. Clinical evidence 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 mmHg drop in systolic
5. Unexplained acidosis pH ≤ 7.3
6. Hypoxaemia, P_aO_2 < 75 mmHg, 9 kPa (breathing room air) or P_aO_2/FiO_2 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 prothrombin time or partial thromboplastin time. Low platelets (<100,000, or 50% drop)
9. Sudden unexplained alteration in mental status
10. High cardiac index >4 l/min/m^2, SVR < 800 dyne s/m^5

pressures less than 90 mmHg. During recovery the mean arterial blood pressure rose to an average of 82 mmHg. All patients during the period of the sepsis syndrome were intubated and all except one receiving intermittent positive pressure ventilation. During recovery, ten remained intubated of which four patients were breathing spontaneously with pressure support (pressure limited triggered ventilation). The severity of illness was assessed by the APACHE II (Acute Physiological and Chronic Health Evaluation) score and TISS (Therapeutic Intervention Scoring System). APACHE II is derived from a combination of physiological variables combined with the Glasgow coma scale and a measure of previous chronic health status.[24] TISS is derived from the number and level of invasiveness of commonly performed intensive care procedures.[25] Both APACHE II and TISS have been widely adopted as measures for quantifying severity of illness and care dependency in critically ill patients. APACHE II was calculated from the worst component values measured in the preceding 24 h.

The patients received a range of sedative agents, analgesics and beta-adrenergic agonists. No subject was receiving any beta-adrenergic blocking or cholinergic blocking agents. Sedation and analgesia was maintained at a level to allow the patients, if at all possible, to respond to verbal commands.

The investigation protocols were reviewed and approved by the Central Oxford Research Ethics Committee.

Data acquisition and analysis: Three adhesive electrodes were applied to the chest wall of each subject to detect the electrocardiogram and measure respiratory excursions by impedance plethysmography. The raw ECG signal (Hewlett Packard, Model No. 78203A) was processed by an algorithm designed to detect and classify the QRS complexes using a multifunction board interfaced with an IBM personal microcomputer (4.77 MHz, 8088 processor and 8087 math co-processor). The respiratory rate was derived from the respiratory impedance signal (Hewlett Packard, Model No. 78212A) obtained from the same ECG electrodes. Approximately 4-min (256 s) blocks of R–R interval data and breath-to-breath impedance data were low pass filtered with a rectangular moving average window of one-half second width and then sampled at 4 Hz. The mean and linear trend of the resulting 1024 point time series was then subtracted, and the power spectra computed from the absolute square of the fast Fourier transform (FFT) of the time series. The spectrum was smoothed with a five-point Hanning window and the spectrum corrected for low pass filter roll-off. At least five, 4-min blocks of data were acquired from each patient during both the sepsis and recovery phases. Heart rate and respiratory rate power spectra were examined between 0.04–1.0 Hz. Figure 1 shows representative examples of HR and RR frequency spectra from a patient during sepsis.

Parameters derived from the heart rate and respiratory spectra included the mean heart rate (HR) and respiratory rate (RR), the power of the heart rate oscillations at the low frequency band (0.04–0.1 Hz, low frequency power or LFP), and at the high frequency band, 0.06 Hz either side of the mode of the corresponding respiratory frequency power spectrum. This high frequency component of the HR frequency spectrum was called the respiratory frequency power or RFP. The power attributed to each component of the frequency

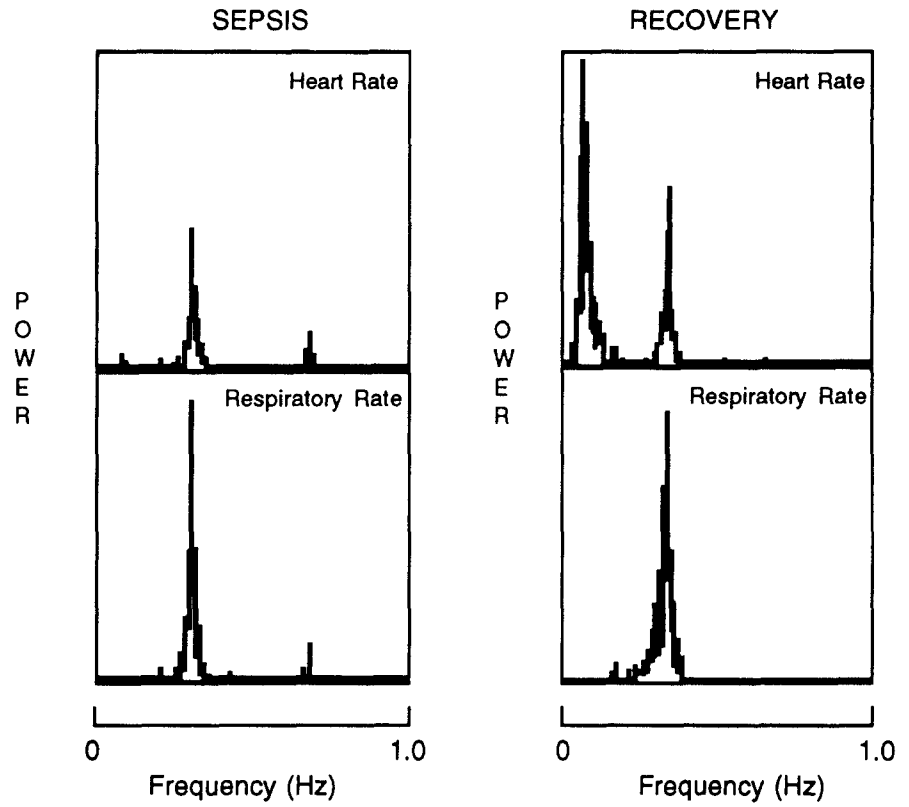

FIG. 1. Examples of heart rate and respiratory rate power spectra (Subject No. 12) during sepsis (right) and recovery (left). Low frequency power (<0.1 Hz) was not detectable during sepsis but returned during the period of recovery.

spectrum was calculated by integration from the area inscribed by each peak within the LFP and RFP frequency domains.

Statistical analysis: Analysis of variance (ANOVA) and the Scheffé multiple range test were used to characterize interactions, and take into account the multiple comparisons of mean values of HR, RR, LFP, RFP and LFP/RFP ratio during sepsis and recovery.[26,27] Log transformations were performed on the LFP and RFP data sets to satisfy the requirement of normal data distribution. LFP and RFP were also expressed as fractions of the total power of the heart rate spectrum (normalized LFP and RFP, LFP_n and RFP_n). Regression analysis was performed by the least squares method. Sympathetic activity relative to parasympathetic activity was indicated by the LFP/RFP ratio or by LFP_n. Statistical significance was established at a level of $p < 0.05$. Mean values are quoted in the text or tables with the standard deviation or 95% confidence limits.

Results

Thirty-nine measurements were made in the 17 subjects (Table 1). Three patients died (Subjects Nos 3, 13 and 17) so that no recovery data was available. Two patients had measurements made only during recovery (Subjects Nos 1 and 6) having fulfilled sepsis criteria 24 h before. Twelve patients had paired data, that is investigations during both the sepsis and recovery periods. Tables 3 and 4 show the results of heart rate spectrum analysis during the sepsis syndrome and during the recovery period. The average time between sepsis and recovery measurements was 3.2 days (range 1 to 14 days).

Analysis of variance: Results are summarized in Table 5. The severity of illness, as reflected by the APACHE II score and TISS, fell from 24 ± 6 to 14 ± 6, $p < 0.0001$ (APACHE II) and from 45 ± 8 to 25 ± 8, $p < 0.0001$ (TISS) between the sepsis and recovery periods. Blood cultures were drawn on all patients on at least one occasion. Four patients had evidence of bacteraemia during the study.

Average heart rate during sepsis (105 ± 20 beats/min) was not significantly different from recovery (106 ± 17 beats/min). Respiratory rate was significantly higher during recovery since patients were allowed to breathe spontaneously during recovery in contrast to sepsis when the patients were largely ventilator dependent and the respiratory rates determined by ventilator settings (22 ± 9 vs. 17 ± 5, $p < 0.02$, Table 5).

Heart rate variability (total spectral power) was significantly lower in sepsis 0.51 ± 0.43 (beats/min)^2. Hz compared to recovery 1.64 ± 1.11 (beats/

Table 3. Sepsis data. Values of low frequency power (LFP, $bpm^2.Hz$), respiratory frequency power (RFP, $bpm^2.Hz$), heart rate (HR, beats per minute), respiratory rate (RR, breaths per minute), total heart rate variability (TotPwr, $bpm^2.Hz$), normalized low frequency power (LFP_n, fraction of total power), LFP/RFP ratio (ratio), APACHE II (P) and TISS scores for the subjects studied *during* the sepsis syndrome

No.	LFP	RFP	HR	RR	TotPwr	LFP_n	logLFP	ratio	AP	TISS
2	0.659	1.050	78	11	1.709	0.386	−0.181	0.628	13	42
3	0.017	0.087	114	12	0.104	0.163	−1.770	0.195	30	60
3	0.042	0.044	114	12	0.086	0.488	−1.377	0.955	26	58
4	0.828	0.224	101	30	1.052	0.787	−0.082	3.696	26	34
5	0.410	0.301	93	17	0.711	0.577	−0.387	1.362	16	38
7	0.422	0.651	92	25	1.073	0.393	−0.375	0.648	22	36
8	0.262	0.200	128	15	0.462	0.567	−0.582	1.310	20	48
9	0.628	0.398	102	12	1.026	0.612	−0.202	1.578	19	35
9	0.155	0.262	102	12	0.417	0.372	−0.810	0.592	23	46
10	0.546	0.136	126	13	0.682	0.801	−0.263	4.015	19	34
11	0.205	0.394	114	14	0.599	0.342	−0.688	0.520	26	46
11	0.188	0.547	126	12	0.735	0.256	−0.726	0.344	31	50
12	0.032	0.388	112	19	0.420	0.076	−1.495	0.082	22	48
12	0.432	0.335	93	19	0.767	0.563	−0.365	1.290	18	49
13	0.010	0.200	130	18	0.210	0.048	−2.000	0.050	41	57
14	0.030	0.348	83	15	0.378	0.079	−1.523	0.086	26	49
14	0.131	0.024	85	14	0.155	0.845	−0.883	5.458	23	34
15	0.310	0.065	91	16	0.375	0.827	−0.509	4.769	19	42
16	0.075	0.094	137	23	0.169	0.444	−1.125	0.798	27	46
16	0.009	0.031	138	20	0.040	0.225	−2.046	0.290	25	43
17	0.006	0.009	89	20	0.015	0.400	−2.222	0.667	31	50
17	0.017	0.114	72	20	0.131	0.130	−1.770	0.149	24	39
Mean	0.246	0.268	105	17	0.514	0.426	−0.972	1.340	24	45
±SD	0.249	0.247	20	5	0.428	0.252	0.688	1.607	6	8

Table 4. Recovery data. Values of low frequency power (LFP, $bpm^2.Hz$), respiratory frequency power (RFP, $bpm^2.Hz$), heart rate (HR, beats per minute), respiratory rate (RR, breaths per minute), total heart rate variability (TotPwr, $bpm^2.Hz$), normalized low frequency power (LFP_n, fraction of total power), LFP/RFP ratio (ratio), APACHE II (AP) and TISS scores for the subjects studied during *recovery* from the sepsis syndrome

No.	LFP	RFP	HR	RR	TotPwr	LFP_n	logLFP	ratio	AP	TISS
1	1.743	0.402	122	12	2.145	0.813	0.241	4.336	6	10
2	2.641	1.106	88	12	3.747	0.705	0.422	2.388	7	26
4	0.836	0.332	106	31	1.168	0.716	−0.078	2.518	8	18
5	0.421	0.080	102	17	0.501	0.840	−0.376	5.262	14	30
6	0.960	1.004	105	40	1.964	0.489	−0.018	0.956	24	24
7	0.620	0.568	88	33	1.188	0.522	−0.208	1.092	15	29
8	0.858	0.188	106	28	1.046	0.820	−0.067	4.564	20	32
9	1.174	0.999	122	12	2.173	0.540	0.070	1.175	18	34
10	0.555	0.720	123	30	1.275	0.435	−0.256	0.771	15	22
11	2.071	2.125	109	14	4.196	0.494	0.316	0.975	21	29
12	1.496	0.235	101	28	1.731	0.864	0.175	6.366	13	29
12	0.297	0.365	78	21	0.662	0.449	−0.527	0.814	16	32
14	0.260	0.117	93	14	0.377	0.690	−0.585	2.222	20	35
14	0.761	0.334	85	13	1.095	0.695	−0.119	2.278	17	28
15	2.650	0.086	105	21	2.736	0.969	0.423	30.814	2	7
16	0.227	0.051	135	26	0.278	0.817	−0.644	4.451	13	22
16	0.956	0.608	132	28	1.564	0.611	−0.020	1.572	11	22
Mean	1.090	0.548	106	22	1.638	0.675	−0.073	4.268	14	25
±SD	0.778	0.529	17	9	1.111	0.165	0.332	7.062	6	8

$min)^2.Hz$, $p < 0.0001$ (Table 5). The fraction of total power within the low frequency domain (LFP_n) was also significantly lower in sepsis (0.43 ± 0.25) than in recovery ($p < 0.68 \pm 0.17$, 0.0012, Table 4, Fig. 2). The ratio RFP/LFP was lower in sepsis (1.34 ± 1.61) than in recovery (4.27 ± 7.06) but not significantly so. LogLFP during sepsis was -0.97 ± 0.69 compared to -0.07 ± 0.33 during recovery ($p < 0.0001$, Table 5, Fig. 2). RFP and logRFP also appeared to be higher during recovery but at lower levels of significance ($p < 0.04$ and $p < 0.05$, Table 5).

Paired *t*-tests were also applied to the twelve patients with both sepsis and recovery datasets. Results were essentially the same as obtained with ANOVA except that RFP and logRFP were no longer significantly different between sepsis and recovery (q.v. Table 5).

Table 5. Results of analysis of variance comparing sepsis and recovery data in 17 subjects

Variable	Mean square	*F*-value	Probability
HR	1.755	0.005	0.9429 (NS)
RR	298.613	6.293	0.0166
LFP	6.826	22.992	0.0001
RFP	0.752	4.821	0.0345
Total Power	12.108	18.985	0.0001
log LFP	7.738	24.468	0.0001
logRFP	1.055	4.425	0.0423
LFP_n	0.591	12.368	0.0012
Ratio	82.202	3.569	0.0667 (NS)
APACHE	927.947	25.879	0.0001
TISS	3643.501	59.194	0.0001

Table 6. Regression analysis of the independent variables APACHE II and TISS against the spectrum analysis dependent variables

Dependent variables	Independent variable-APACHE II		Independent variable-TISS	
	r value	Probability	*r* value	Probability
HR	0.143	0.3843 (NS)	0.025	0.8820 (NS)
RR	0.133	0.4211 (NS)	0.403	0.0110
LFP	0.672	0.0001	0.705	0.0001
RFP	0.178	0.2790 (NS)	0.243	0.1367 (NS)
Total Power	0.550	0.0003	0.602	0.0001
log LFP	0.746	0.0001	0.745	0.0001
log RFP	0.267	0.1000 (NS)	0.267	0.1004 (NS)
LFP_n	0.661	0.0001	0.670	0.0001
Ratio	0.504	0.0011	0.526	0.0006

Regression analysis: APACHE II scores during sepsis and recovery showed significant, inverse correlations with LFP, Total Power, logLFP, LFP_n and the LFP/RFP ratio (Table 6, Fig. 3). TISS showed similar correlations with the spectral analysis variables except that there was now a significant correlation with RR (Table 6, Fig. 4). APACHE II and TISS were highly correlated with an r value of 0.813 ($p < 0.0001$).

There were no significant correlations between HR, RR or RFP and APACHE II ($r = 0.143$, $r = 0.133$, $r = 0.1178$). TISS showed no correlation with HR or RFP ($r = 0.025$, $r = 0.243$) but

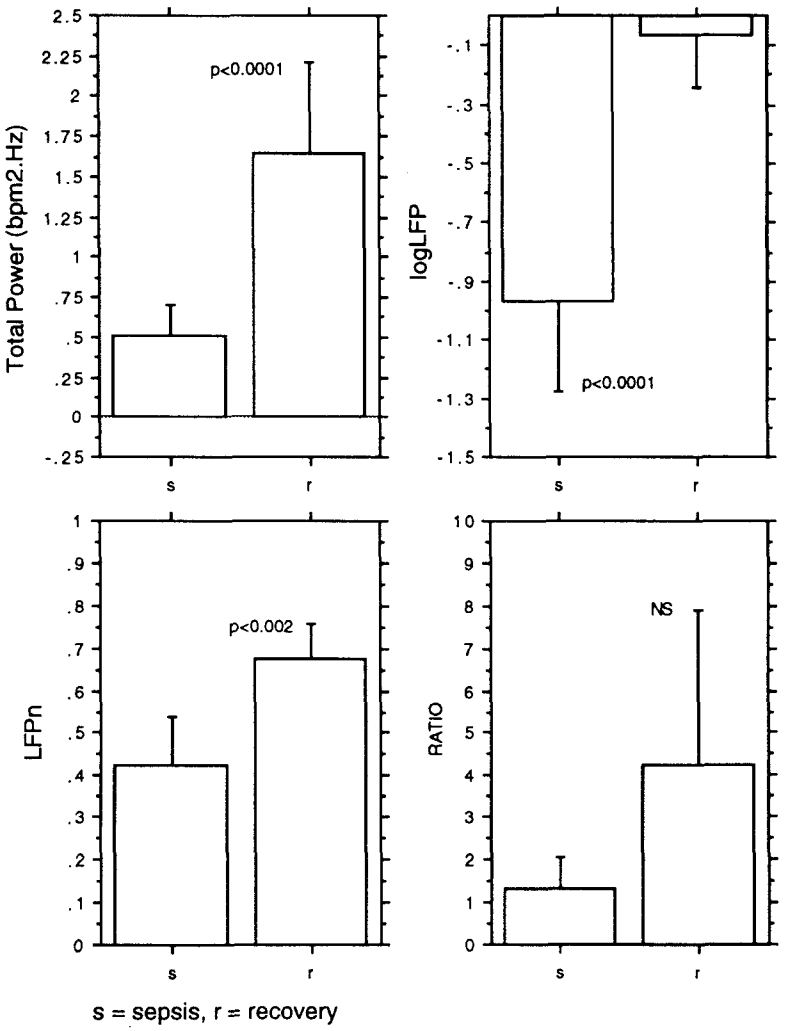

FIG. 2. Analysis of variance comparing total heart rate variability (Total Power), normalized low frequency power (LFP_n, fraction of total power), logarithm of low frequency power (logLFP) and LFP/RFP ratio (ratio) during sepsis and recovery in 17 patients. Error bars represent the 95% confidence limits.

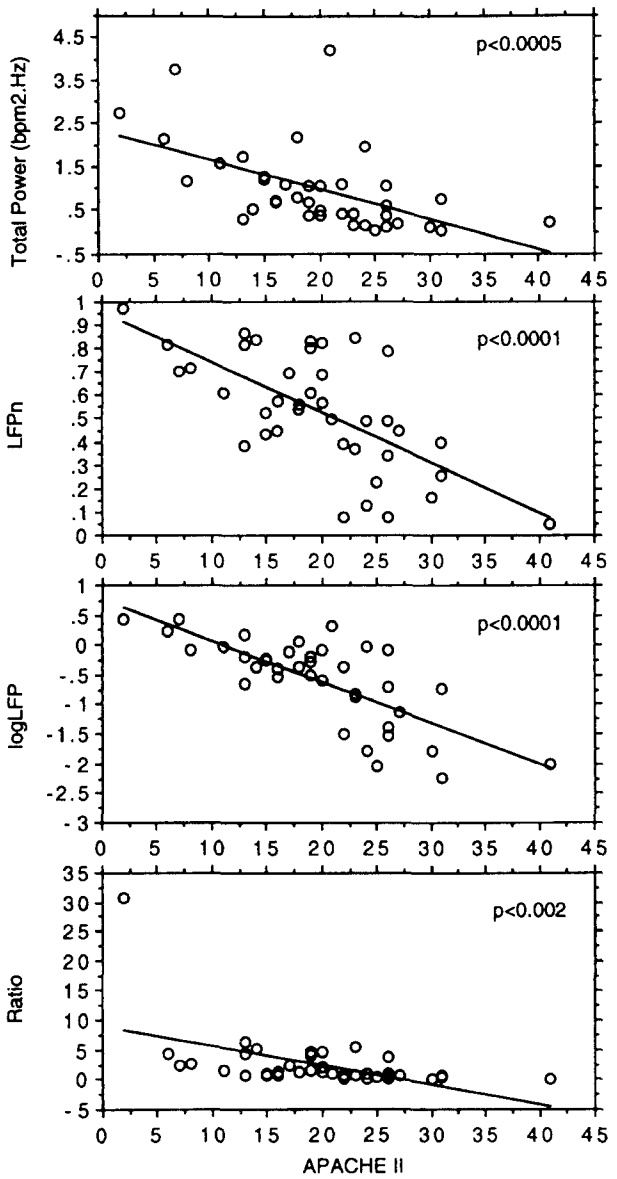

FIG. 3. Regression analysis of APACHE II values against the dependent variables total heart rate variability (Total Power), normalized low frequency power (LFP_n, fraction of total power), logarithm of low frequency power (logLFP) and LFP/RFP ratio (ratio).

was inversely and relatively weakly correlated with RR ($r = -0.403, p < 0.02$).

Concomitant medication: Sedation and analgesia were maintained with combinations of morphine, alfentanyl, midazolam or propofol and was the same in both sepsis and recovery in all but three subjects. Statistical re-analysis by ANOVA after omission of these three subjects showed essentially the same results except that there was now a statistically significant increase in LFP/RFP ratio during recovery.

Inotropic and pressor support were maintained with combinations of dobutamine, adrenaline (epinephrine) and noradrenaline (norepinephrine). Dopamine was used in doses of less than 2.5 μg/kg/min to maintain renal perfusion. Eight patients were receiving neither inotropic nor pressor support (except for the *same* dopamine doses) during sepsis and recovery. Analysis of variance of these eight patients' data showed the same trends for LFP_n and LFP/RFP ratio (NS) and significant increases in total power ($p < 0.01$) and logLFP ($p < 0.003$) during recovery as with all 17 patients. The mean heart rate for these eight patients was unchanged between sepsis and recovery.

Discussion

This is the first report of a reduction in heart rate variability and its sympathetic component (LFP_n) during the sepsis syndrome. The results of ANOVA (comparing sepsis and recovery) were supported by regression analysis using APACHE and TISS as independent variables (Table 6). Regression analysis clearly showed a fall in overall and sympathetically mediated heart rate variability with increasing severity of illness (APACHE II and TISS). The disturbance in autonomic control of heart rate variability could result from alterations in vasomotor activity within the central nervous system, from impairment of neuronal transmission to the heart or from changes in end organ responsiveness.

Alterations in autonomic regulation of heart rate have been previously described in several disease models. For example, the reduced heart rate variability in diabetes mellitus[21,28,29] and the absence of heart rate variability in the heart transplant recipient[30,31] illustrates the effect of impaired or interrupted neuronal transmission. In contrast, the reduced spectral power of heart rate variability in severe congestive cardiac failure is probably due to reduced end organ response.[10,11,13,14,32]

Reduced heart rate variability may have a prognostic value in certain situations. For example, in patients following myocardial infarction, low heart rate variability is associated with higher mortality.[33] Similarly, reduced sympathetically mediated heart rate variability in children recovering from cardiac surgery has been shown to predict a fatal outcome.[34] It is interesting that sympathetically modulated heart rate variability was *reduced* in our hypotensive septic patients while increased low frequency (predominantly sympathetic) variability in heart rate variability has been demonstrated in non-sepsis related hypotension.[35] This latter effect would be consistent with the expected homeostatic response in an intact and unimpaired, autoregulatory mechanism.[36]

Myocardial dysfunction in the sepsis syndrome. Cardiovascular features of the sepsis syndrome are particularly prominent and have a major effect upon

clinical outcome.[4,8] Characteristically the cardiovascular system is hyperdynamic with an increased cardiac index and low systemic vascular resistance.[37–40]

Evidence of myocardium dysfunction, as part of the haemodynamic response to sepsis and endotoxaemia, has been more difficult to identify because of coincident alterations in preload, afterload, left ventricular diastolic compliance and sympatho-adrenal effects. However, much evidence points towards the early development of myocardial dysfunction in the sepsis syndrome.

It is unlikely that a direct toxic effect of the endotoxin molecule on the beta-adrenergic receptor is responsible for myocardial dysfunction in sepsis[41] but other mediators, such as the leukotrienes may play a role.[42,43] The existence of a myocardial depressant factor has been supported in a number of studies although the specific agent has yet to be identified.[40,44] Such myocardial depressant agents produce a reversible decrease in left ventricular ejection fraction and ventricular dilation.[40,44] However, other mediators of sepsis, such as TNF, PAF and the leukotrienes, may also affect myocardial contractility. TNF produces myocardial depression in animals[45,46] and in humans where the effect can be transiently reversed by antibody directed against TNF.[47] PAF exerts a negative inotropic effect on the heart and may lower arterial blood pressure.[48] In addition, the leukotrienes C4, D4, and E4 decrease coronary blood flow[49] and appear to be important myocardial depressants.[43] In humans, administration of interleukin-2 (IL-2) has also been found to decrease arterial pressure, systemic vascular resistance and ventricular ejection fraction.[50] Any of these factors, by reducing myocardial and therefore sinus node responsiveness could result in reduced heart rate variability.

Beta-receptor down-regulation: Down-regulation of beta-receptors has been recognized in non-sepsis related heart failure for some time and is usually associated with a reduction in beta-adrenergic receptor density, adenyl cyclase concentration or creatine kinase concentration.[51–54] It is possible that myocardial dysfunction in sepsis is also associated with some degree of beta-adrenergic receptor down-regulation. Endogenous noradrenaline has been shown to produce beta-adrenergic receptor down-regulation in dogs. The chronic elevation of noradrenaline levels produces desensitization that is characterized not by decreased beta-adrenergic receptor density, but by reduced adenylate cyclase activation and uncoupling of the beta-adrenergic receptor.[55] An analogous clinical model can be found in patients with cardiomyopathy associated with phaeochromocytoma. Following resection of the tumour, recovery of myocardial function appears to return within days.[56] The adrenergic agents dobutamine and pirbutalol also induce beta-receptor down-regulation but by a different mechanism.[57,58]

Release of endogenous opioids in shock may also reduce beta-receptor responsiveness; an effect that can be reversed by naloxone and which has promoted the use of that drug in shock syndromes.[59] Down-regulation of beta-adrenergic receptors may occur in asthmatic patients[60] and is associated with a reduction in sympathetically mediated heart rate variability.[61] This phenomenon may be an inherent pathophysiological feature of asthma or may be due to the effects of treatment with adrenergic bronchodilators.

In a similar way it would be reasonable to suspect beta-adrenergic inotropes and arterial pressor agents to have induced a degree of down-regulation in the septic patients presented in this paper. However, similar effects were seen in low frequency heart rate variability in the eight patients who received only renovascular doses of dopamine both during sepsis and recovery. Thus, the prescription of exogenous adrenergic agents could not have entirely explained the differences in sympathetically mediated heart rate variability between sepsis and recovery in those eight patients, although it is possible that could have contributed to some degree.

Two other mechanisms for depressed sympathetic modulation of heart rate need to be considered. The first involves sepsis-related polyneuropathy, which could impair neuronal transmission to the heart in the sepsis syndrome.[62] The second relates to a possible direct effect of endotoxin upon the central nervous system. The latter may explain the obtundation observed clinically during sepsis as well as reduced central sympathetic outflow demonstrated in animal models of sepsis.[63]

Parker *et al.* have shown that septic patients with high mean heart rates are at greater risk of death or major complication. Of the three patients who died in our study, Subject No. 13 had the highest APACHE II score (41 points) and the highest heart rate (130 beats per minute). However, regression analysis of HR against APACHE II failed to demonstrate a significant correlation. It remains to be seen whether more regular assessment of heart rate variability during sepsis may provide data of prognostic value.

Care should be exercised when interpreting HRSA data since the basal mean respiratory and heart rate significantly influence both the RFP and LFP data.[16,64] Although ANOVA showed RFP and logRFP to be higher during recovery from sepsis this was not confirmed by *t*-test nor did regression analysis show a relationship to severity of illness (Table 6). However, it is possible that the higher

mean respiratory rate during recovery from sepsis could have partially obscured the recovery increase in RFP.[64] On the other hand, review of the respiratory rate data does not confirm any consistent effect upon RFP. In six patients, in whom there was less than 2 breaths/min difference in respiratory rate between sepsis and recovery periods (Subjects Nos 2, 4, 5, 11 and 14) there were no discernible trends. In two patients RFP was unchanged, in one RFP rose and in three, it fell. In the remaining five subjects in whom respiratory rates fell significantly, RFP rose in three (Subjects Nos 7, 8 and 12) and fell in two (Subjects Nos 10 and 15).

The average heart rates were not significantly different between sepsis and recovery (105 ± 20 beats/min vs. 106 ± 17 beats/min) so would not be expected to affect RFP or LFP values. Also, by expressing LFP data as a percentage of total variability (LFP_n) the effect of mean heart rate upon the heart rate spectrum components is largely avoided.[16]

Sedation and analgesia can have a significant effect upon heart rate variability. In a recent study, we have demonstrated that both propofol and thiopentone anaesthesia reduce overall heart rate variability but leave sympathetic/parasympathetic balance undisturbed.[65] It is unlikely that sedation was responsible for the differences between sepsis and recovery since the fall in LFP_n was apparent even in those subjects receiving the same levels of sedation for both the period of sepsis and recovery. Sedation may have reduced the total level of heart rate variability compared to healthy volunteers[61] although the greater age of the patients in this present study would also be a contributing factor reducing heart rate variability.[66] Other factors that could influence both sympathetically and parasympathetically mediated heart rate variability, such as diabetes or pre-existing renal or cardiac disease, were not present in any of our subjects.

We have shown that total heart rate variability and its sympathetic component are reduced during the sepsis syndrome. The mechanism is unclear but could be due to impaired central nervous system sympathetic outflow, a sympathetic neuropathy, or mediator effects upon cardiac adrenergic receptors. Several mediators known to contribute to the clinical and pathophysiological features of sepsis could down-regulate myocardial responsiveness. Further studies utilizing antagonists to endotoxin, TNF or the interleukins may shed light on the underlying mechanisms.

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