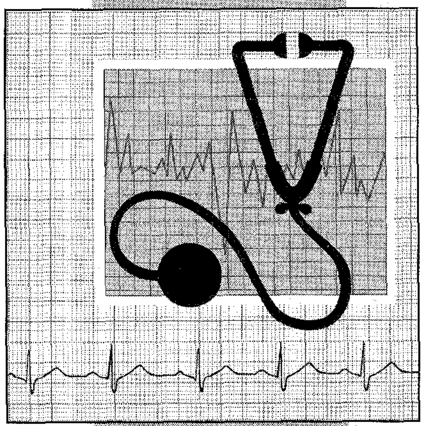

Monitoring the Autonomic Nervous System in the ICU Through Cardiovascular Variability Signals

Assessing ICU Patient Status Using Spectral Analysis Parameters

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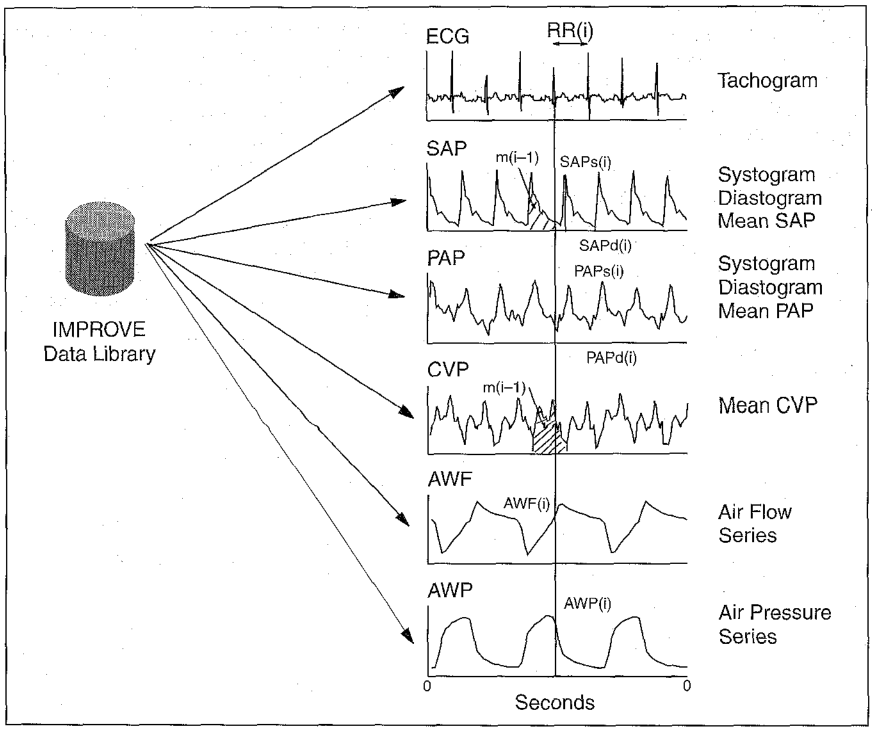
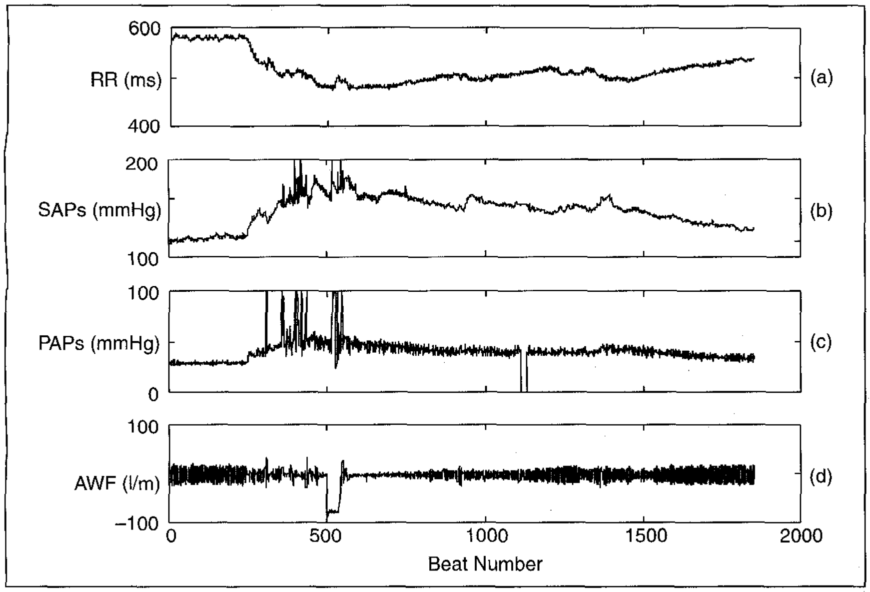
The beat-to-beat fluctuations of the RR interval series obtained from the ECG signal (called heart-rate variability (HRV)) and from the systemic arterial pressure (SAP) signal are ruled by complex neural mechanisms under control of the autonomic nervous system (ANS). The spectral analysis of HRV and SAP variability signals may provide a quantitative and noninvasive measure of the activity of the ANS [1-4]. In fact, two major spectral components are commonly found on the HRV spectra. The low-frequency (LF) component, centered around 0.1 Hz, increases in the presence of sympathetic stimuli [5], while the high-frequency (HF) component, synchronous with respiration, is mainly modulated by parasympathetic (vagal) control [6-7]. Furthermore, their values accurately reflect the state of the sympatho-vagal balance [8]. SAP variability shows similar oscillations, which have been linked to sympathetic modulation of vasomotor activity (LF



1. Raw signals and derived beat-to-beat series extracted from the IMPROVE data library.



2. Beat-to-beat variability series obtained during airway suction. Data are from record #40. (a) RR tachogram, (b) systogram from SAP, (c) systogram from PAP, and (d) respiratory series from AWF.

power in SAP spectrum) [9-11] and to respiration (HF) mainly through its mechanical effects [12]. Similar rhythms are seen also in other signals of cardiovascular origin, such as peripheral flow [13] and central venous pressure (CVP) [14], thus suggesting the widespread influence of autonomic control on circulation.

Although linear models may explain HR and SAP dynamics [15], some nonlinear processes are certainly involved [4, 16, 17]. Recent findings on fractal systems have documented processes that are characterized by self-similarity patterns and that show Fourier spectra that are non-flat and have $1/f^{\alpha}$ power distribution; that is, the spectra have inverse proportionality to the frequency values with a scaling law defined by α. This 1/f distribution has been verified in many biological and physiological systems. The initial evidence of 1/f behavior was reported for the human HRV signal [18] and then confirmed by [19] and [20] for arterial blood pressure in dogs. Under normal conditions, index α shows values near 1, confirming the broad-band nature of the spectrum, while α increases in the presence of pathological cardiovascular events. The power law regression parameter, α -slope, may predict the risk of death in patients after myocardial infarction [21, 22].

In this article, we aim to study the usefulness of cardiovascular variability parameters for monitoring intensive-care unit (ICU) patients. Previous results have associated significant changes in HRV parameters to several cardiological and noncardiological diseases [4]. Moreover, patients who had a favorable course after myocardial infarction presented higher values of HRV, leading to the conclusion that an augmented HRV may be protective against cardiac mortality and sudden cardiac death [4]. In ICU patients, the decrease in the total power and the lack of sympathetic modulation was associated with increased mortality [23]. During sepsis syndrome, the total HRV and the sympathetic mediated component were significantly lower with respect to the control phase [24]. In addition, human endotoxemia was connected with a loss of physiological beat-to-beat variability [25].

In this study, both long-term and short-term spectral parameters [4] are investigated. Long-term variability is assessed through the evaluation of the α-slope on beat-to-beat 24-h spectra, and the results are correlated to the patient outcome. Short-term variability parameters

Table 1. List of patients included into the study. D: deceased; S: survived.

Patient #	DL Record	Age (years)	Gender	Emergency/ Elective	ICU Days	ICU Outcome	Weight (Kg)	Height (cm)	Main Disorders During Study
1	9, 11, 12	34	Male	Emergency	33	D	165	176	High flow state, O_2 content related problems
2	19	27	Male	Emergency	24	D	103	185	High flow state
3	27	47	Male	Emergency	13	S	75	175	High flow state, O_2 content related problems
4	32, 34	69	Male	Emergency	21	D	93	172	High flow state
5	35	18	Male	Emergency	6	S	63	178	—
6	36	78	Male	Elective	19	S	80	169	—
7	37	39	Male	Emergency	12	D	90	185	High flow state, O_2 content related problems
8	40	56	Female	Emergency	32	D	65	170	Hypovolemia, O_2 content related problems
9	45	59	Male	Emergency	3	S	85	190	Cardiac failure, O_2 content related problems
10	46	66	Male	Elective	16	D	80	172	High flow state, O_2 content related problems
11	47	38	Male	Emergency	17	S	70	170	Hypovolemia, high flow state, O_2 content related problems
12	48	13	Female	Emergency	5	S	65	165	—
13	50	55	Male	Emergency	8	D	85	173	High flow state, O_2 content related problems
14	57	72	Male	Elective	11	S	66	162	O_2 content related problems
15	58	47	Male	Emergency	6	S	80	180	O_2 content related problems

are calculated before, during, and after an airway suction (AWS) maneuver, which is a common procedure in intensive care. It is used to clean the patients airway from mucous secretions during respirator-controlled ventilation, thus improving gas (oxygen/carbon dioxide) exchange at alveolar level. During AWS, severe pain and tracheal irritation, which, in turn, induce coughing against the ventilator and increase airway pressure, are supposed to provoke a sympathetic activation. The short-term variability parameters, which are computed in different time epochs around the AWS, may be employed during these events for advanced monitoring of ANS responses to this therapeutic intervention.

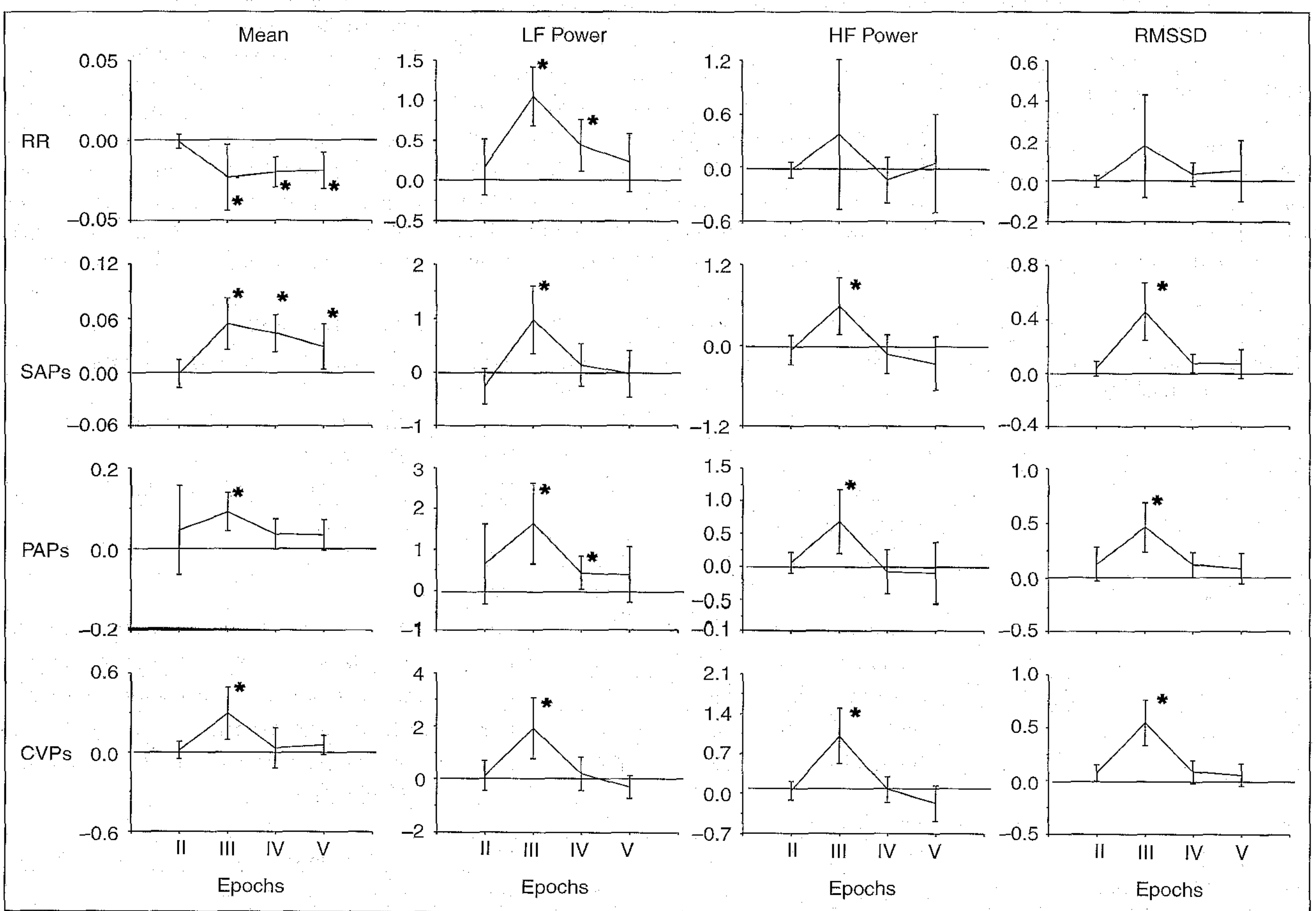
Methods

Series Extraction

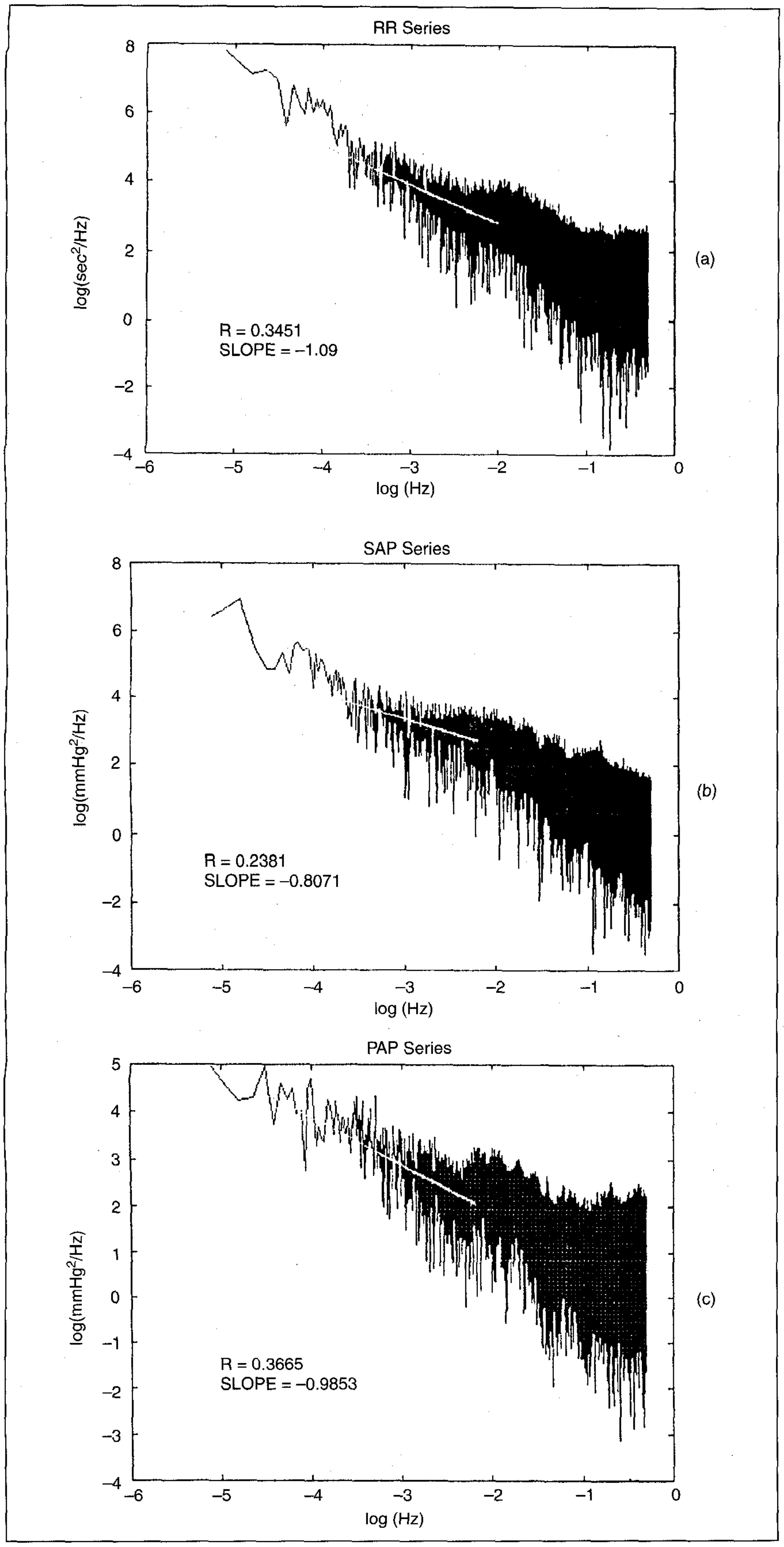
All data were extracted from the IMPROVE data library (DL) [26-27]. The beat-to-beat variability series, obtained from the raw signals of the DL, contained traditional measures such as RR interval tachograms from ECGs, systograms (SAPs, i.e., the beat-to-beat values of systolic arterial pressure), diastograms (SAPd, i.e., the beat-to-beat values of diastolic arterial pressure) series from the systemic arterial pressure, and respiration-related series from airway pressure (AWP) and airway flow (AWF) signals. In addition, other beat-to-beat measures were computed from pulmonary arterial pressure (systolic (PAPs) and diastolic (PAPd) values) or from the CVP signal (mean values (CVPm)).

QRS detection and RR interval measurements were automatically performed by a derivative/threshold algorithm [28]. Because of the low sampling rate (100 Hz), we performed a QRS parabolic interpolation and we measured the RR interval as the distance between the maximum of two successive interpolating parabolas, thus reducing the influence of low sampling rate [29-30]. The accuracy in QRS detection, the absence of missed or misdetected beats, or the presence of artifacts, were visually checked and corrected by the operator using a commercially available software (Cardioline Remco Italia, AD35 Top). Each beat was automatically classified (normal, ventricular, artifact) and the code was used to improve the successive analysis.

The position of the R wave was used as a reference point for the extraction of the other beat-to-beat series. In particular, the systogram and the diastogram were obtained on both systemic and pulmonary pressures by measuring the systolic and the diastolic values inside the cardiac cycle (see Fig. 1). The beat-to-beat CVP series was extracted by computing the mean value inside the cardiac cycle. To reduce noise, CVP, SAP, and PAP signals were low-pass filtered (cut-off frequency 15 Hz) before extracting the beat-to-beat series. Finally, two respiratory-related series were obtained by sampling the airway pressure and the airway flow signals in correspondence with the QRS complex on the ECG. Respiratory signals were previously filtered by a low-pass filter (cut-off frequency 0.5 Hz), in order to reduce artifact and noise and to avoid aliasing.



3. Global results obtained from the population studied. For each parameter, the mean difference change from the basal values are plotted in each epoch considered. The 95% CI are superimposed. Values are in dB units (see text for details); * $p < 0.05$.



4. Examples of 1/f spectrum from (a) RR interval, (b) SAPs and (c) PAPs series. The linear log-log regression is superimposed in the range 10^{-4}-10^{-2} Hz. Both slope and regression coefficients are shown.

Spectral Analysis

Spectral analysis was performed by means of a parametric approach based on the autoregressive (AR) model. In this approach, the signal, $y(t)$, is seen as the output of an AR model of p order, and its spectrum can be computed as:

$$P(f) = \frac{\sigma^2 \Delta t}{\left|1 - \sum_{k=1}^{p} a_k z^{-k}\right|^2_{z=\exp(-j2\pi f\Delta t)}} = \frac{\sigma^2 \Delta t}{\left|\prod_{i=1}^{p} (1 - z_i z^{-k})\right|^2_{z=\exp(-j2\pi f\Delta t)}}$$

where a_k $\{k=1,2,\ldots,p\}$ are the model coefficients, σ^2 is the variance of the white-noise process feeding the model, Δt is the sampling interval ($\Delta t = 1$, for RR tachogram series), and z_is are the poles of the model. The spectral estimation is obtained from the identification of model coefficients. Several techniques do exist that make it possible to identify the model coefficients that give the best fit of the data, $y(t)$ [31]. From the evaluation of the model poles, it is possible to divide the spectrum into bell-shaped curves, in correspondence with each spectral peak, and to compute the values of power, P_i, and frequency, f_i, of each spectral component from the position and the residual, r_i, of each pole:

$$f_i = 2\pi \mathrm{arctg}(\mathrm{Im}(z_i)/\mathrm{Re}(z_i))$$
$$r_i = z^{-1}(z - z_i)P(z)\Big|_{z=z_i}$$

The power, P_i, becomes 2 Re (r_i) σ^2 in the case of complex conjugate pole pairs, and Re(r_i) in the case of a real pole [32-34]. In this article, parametric estimation was obtained through the Levinson-Durbin algorithm, while model order was automatically selected through AIC (Akaike Information Criteria [35]), among those orders that guarantee the whiteness of the prediction error [36].

1/f Parameters

Systems with periodic or quasi-periodic behavior have spectra that show a small number of components, while broad-band spectra are generally characterized by more complex patterns, which are typical of stochastic noise or deterministic chaos. A particular broad-band spectrum has power values that scale with the frequency, according to the following law:

Table 2. Parameters extracted (mean ± sd) during the different epochs considered. 95% confidence intervals (CI) of the mean are also reported.

	Mean	CI	RMSSD	CI	LF power	CI	HF power	CI
RR INTERVAL								
	(ms)	(ms)	(ms)	(ms)	(ms^2)	(ms^2)	(ms^2)	(ms^2)
I	606.24±90.65	575.1; 637.38	7.37±12.28	3.16; 11.59	14.49±17.38	8.51; 20.46	21.87±90.63	-9.26; 53.0
II	601.48±86.64	571.72; 631.24	8.45±15.78	3.03; 13.87	43.02±96.06	10.02; 76.01	25.12±96.4	-8.0; 58.23
III	576.69±72.72	551.71; 601.67	20.63±62.77	-0.93; 42.19	552.39±2272.6	-228.3; 1333.08	597.36±3270.374	-526.05; 1720.77
IV	581.86±85.62	552.45; 611.27	11.51±22	3.95; 19.07	30.2±42.97	15.44; 44.96	37.8±122.48	-4.28; 79.87
V	586.01±86.66	556.24; 615.78	11.73±20.44	4.71; 18.75	26.12±38.45	12.91; 39.32	65.83±181.61	3.45; 128.22
SAPs								
	(mmHg)	(mmHg)	(mmHg)	(mmHg)	($mmHg^2$)	($mmHg^2$)	($mmHg^2$)	($mmHg^2$)
I	110.13±18.01	103.95; 116.32	3.6±4.95	1.9; 5.3	8.73±16.88	2.93; 14.53	11.08±20.28	4.11; 18.04
II	112.15±19.77	105.36; 118.94	5.26±7.79	2.58; 7.94	9.59±19.2	3.0; 16.19	13.36±22.9	5.5; 21.23
III	133.56±30.01	123.25; 143.87	11.6±8.89	8.55; 14.65	108.03±115.24	68.45; 147.62	58.16±72.03	33.42; 82.90
IV	125.63±25.9	116.74; 134.53	6.23±10.05	2.78; 9.69	13.68±26.1	4.71; 22.64	18.89±36.85	6.22; 31.54
V	118.21±20.32	111.23; 125.19	5.67±8.47	2.76; 8.58	8.59±11.38	4.68; 13.0	14.67±27.84	5.10; 24.23
PAPs								
	(mmHg)	(mmHg)	(mmHg)	(mmHg)	($mmHg^2$)	($mmHg^2$)	($mmHg^2$)	($mmHg^2$)
I	27.37±17.11	20.86; 33.88	3.19±1.56	2.59; 3.78	0.19±0.25	0.09; 0.28	3.29±3.05	2.13; 4.45
II	32.03±26.65	21.9; 42.17	5.76±7.39	2.95; 8.57	283.19±1494.6	-285.35; 851.73	28.37±120.49	-17.46; 74.2
III	37.46±20.94	29.49; 45.42	12.35±7.59	9.47; 15.24	105.98±124.13	58.76; 153.19	52.82±66.08	27.68; 77.95
IV	31.02±18.36	24.03; 38.0	5.2±2.96	4.07; 6.33	0.75±1.35	0.23; 1.26	5.6±8.01	2.55; 8.65
V	28.73±17.82	21.96; 35.51	4.32±2.18	3.48; 5.15	1.96±8.24	-1.17; 5.09	4.05±4.54	2.32; 5.78
CVP								
	(mmHg)	(mmHg)	(mmHg)	(mmHg)	($mmHg^2$)	($mmHg^2$)	($mmHg^2$)	($mmHg^2$)
I	3.35±5.31	1.44; 5.27	1.02±0.47	0.86; 1.19	0.16±0.41	0.01; 0.3	0.54±0.48	0.37; 0.71
II	4.18±5.54	2.18; 6.18	1.79±2.33	0.95; 2.63	5.9±20.98	-1.67; 13.46	1.88±4.58	0.23; 3.53
III	9.46±7.26	6.84; 12.08	6.28±3.63	4.97; 7.59	71.96±79.6	43.26; 100.66	19.06±27.59	9.11; 29.0
IV	4.16±5.3	2.25; 6.07	1.46±1.06	1.07; 1.84	2.78±11.23	-1.27; 6.83	0.88±1.42	0.37; 1.39
V	3.91±5.54	1.91; 5.9	1.32±0.8	1.03; 1.61	4.23±20.75	-3.25; 11.71	0.92±1.8	0.27; 1.57

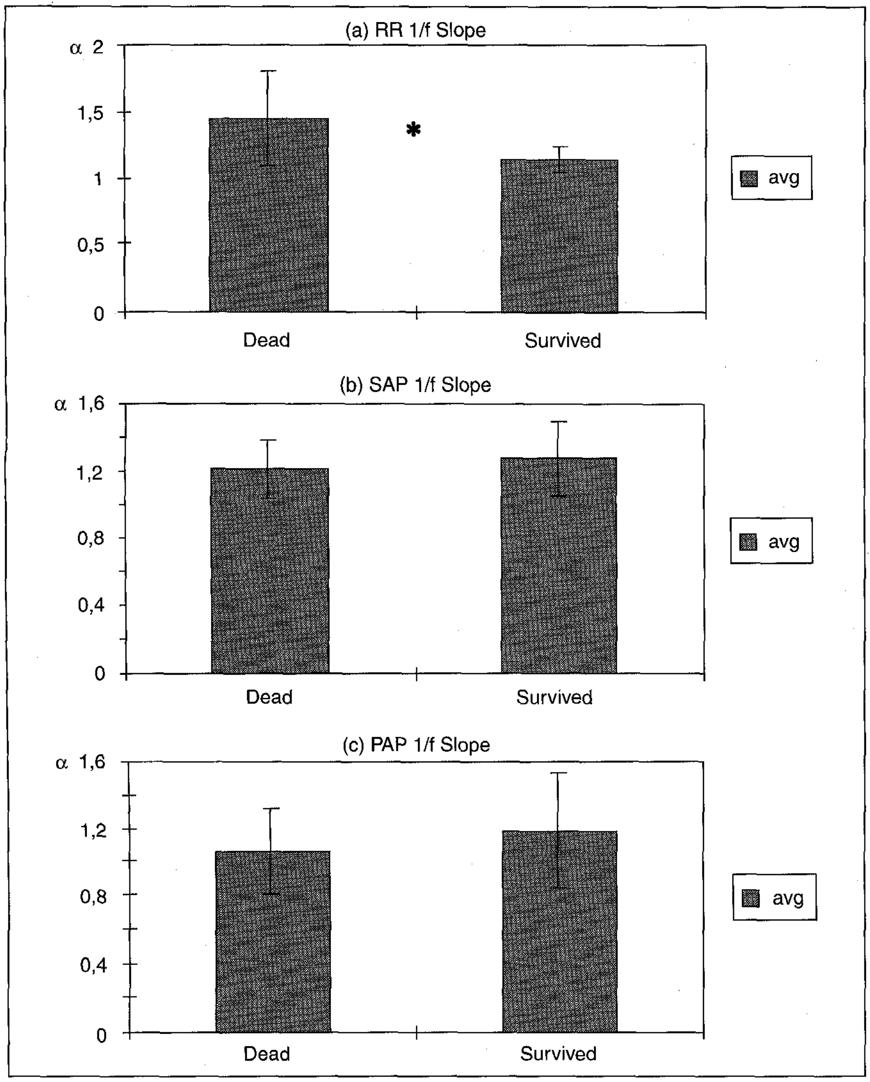
$$P(f) = f^{-\alpha}$$

where α is a constant. In the range $1<\alpha<3$, the curve has noninteger (fractal) dimension. A power-law spectrum of this kind does not possess a privileged time scale and is typical of a fractal process [37].

For each patient, a single power spectrum was calculated on the whole data record by using the fast Fourier transform algorithm. After plotting the spectrum on a log-log scale, the log (power) was regressed on log (frequency) in the range between 10^{-4} and 10^{-2} Hz. The α parameter was obtained as the slope of the regression line on the power spectrum for time-series length exceeding 90,000 points.

No filtering procedures were performed, maintaining the original integrity of the data. Possible presence of high-frequency artifacts, such as those induced by ectopic beats, only slightly affect the results, as the analysis is mainly concerned with the very LF (VLF) and ultra LF (ULF) components (up to 10^{-2} Hz).

Despite of the apparent simplicity of the method, which does not require any *a priori* hypothesis, this approach has demonstrated a powerful capability in the global evaluation of time-series properties [21-22]. Different and more complicated methods exist for estimating the long-range dependence and self-similarity of time series [38]. Some of these are particularly useful to confirm the long memory characteristics in biological processes, as the behavior of VLF and ULF component in cardiovascular variability series seems to suggest.



5. Mean and standard deviation values of the α-slope parameters as obtained for the study population on (a) RR, (b) SAP, and (c) PAP spectra.

Patient and Event Selection

Data for the IMPROVE DL were collected from a heterogeneous ICU patient population. The various diagnoses and medications may differently influence the beat-to-beat HRV parameters. We therefore decided to focus the short-term analysis on a common repetitive stimulus such as the AWS. In order to reduce the effect of confounding variables, the DL annotations were screened by clinical experts. At least the 30 minutes preceding the selected AWS had to be free from nursing activities and changes in the rate of vasoactive drug infusion. We selected 15 patients out of the 59 recordings of the DL. Patients had various courses of illness and both positive and negative outcomes. The demographic data are shown in Table 1. The selected population had no arrhythmias, no rhythmic dysfunctions that might

Table 3. Mean spectral parameters from records #56, #59a, and #59b of the DL.

	Mean RR	Variance	LF power	HF power
Basal conditions	686.3 0±24.9	19.88±16.39	4.15±3.68	4.12±3.34
12 days later 11.13-12.13	806.88±22.03	44.88±19.9	4.12±5.60	4.44±2.83
12 days later 12.13-13.13	855.40±16.36	65.61±21.54	0.80±1.3	8.41±8.24
12 days later 13.13-14.13	781.69±14.26	35.91±20.17	1.59±1.41	3.26±3.51
12 days later 14.13-15.13	784.00±17.00	29.07±26.03	0.30±0.20	2.07±2.01
12 days later 15.13-16.13	838.84±8.38	10.00±9.40	0.29±0.29	1.76±0.59
12 days later 16.13-17.13	838.01±0.75	4.87±1.24	—	1.62±0.51
12 days later 17.45-18.15	855.33±1.76	6.92±4.60	—	2.31± 2.00

alter the variability analysis, and good quality of their ECG and pressure signals during and after AWS.

For analysis of the suction periods, different time epochs were defined. They included five periods centered around each episode: Period I or basal period (roughly 20 minutes before the beginning of the suction), period II (in the five minutes preceding the suction), period III (during AWS), and finally periods IV and V (5 and 10 minutes after the end of AWS, respectively). In these periods, the simultaneous presence of pseudo-stationary segments on all the beat-to-beat series were manually annotated by an operator through interactive software and then used for the successive analysis. Because the number of suction periods varied among the patients, we considered only one suction period for each patient for statistical analysis.

Statistical Analysis

Spectral parameters show a great interindividual spread of values. Therefore, a normalization procedure is required to make the data comparable. The procedure used in this article is a decibel (dB) transformation of the data, with individualized baselines. This transformation has two advantages: 1) it makes the indexes directly comparable and 2) the logarithmic transformation, inherent in decibel measure, reduces skewness of the variables. Data were transformed according to the following expression (baseline values were different for different patients):

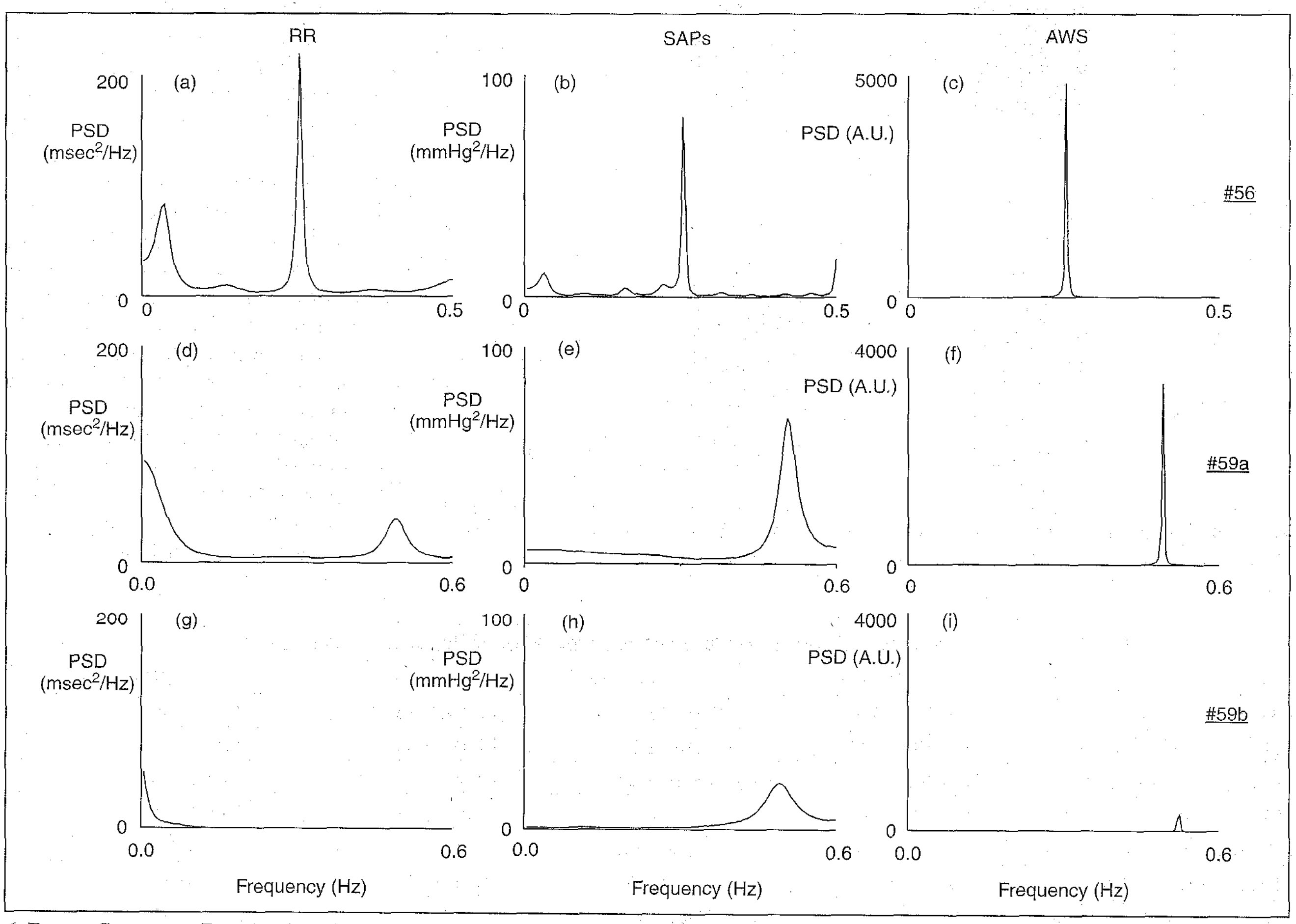
dB change from baseline = log(current value/baseline))

Mean values of dB-transformed data and the 95% confidence interval (CI) of the mean were computed for every variability parameter in each epoch considered. It is worth noting that with a number of cases ($n > 10$), the absence of overlap between two confidence limits indicates that the two sample means differ at the specified level of confidence [39]. Regression analysis and paired *t*-test were used as necessary. Statistical significance was accepted when $p < 0.05$.

Spectral parameters show a great interindividual spread of values.

Results

The section is divided in three parts; the first two are dedicated to presentation of the results obtained from short-term and long-term analysis while the third



6. Power Spectrum Density (PSD) for RR tachogram (a,d,g), systogram (b,e,h) and AWF (c,f,i) in different epochs for the same patient. Data were divided into separate files in the DL (#56, #59a, #59b).

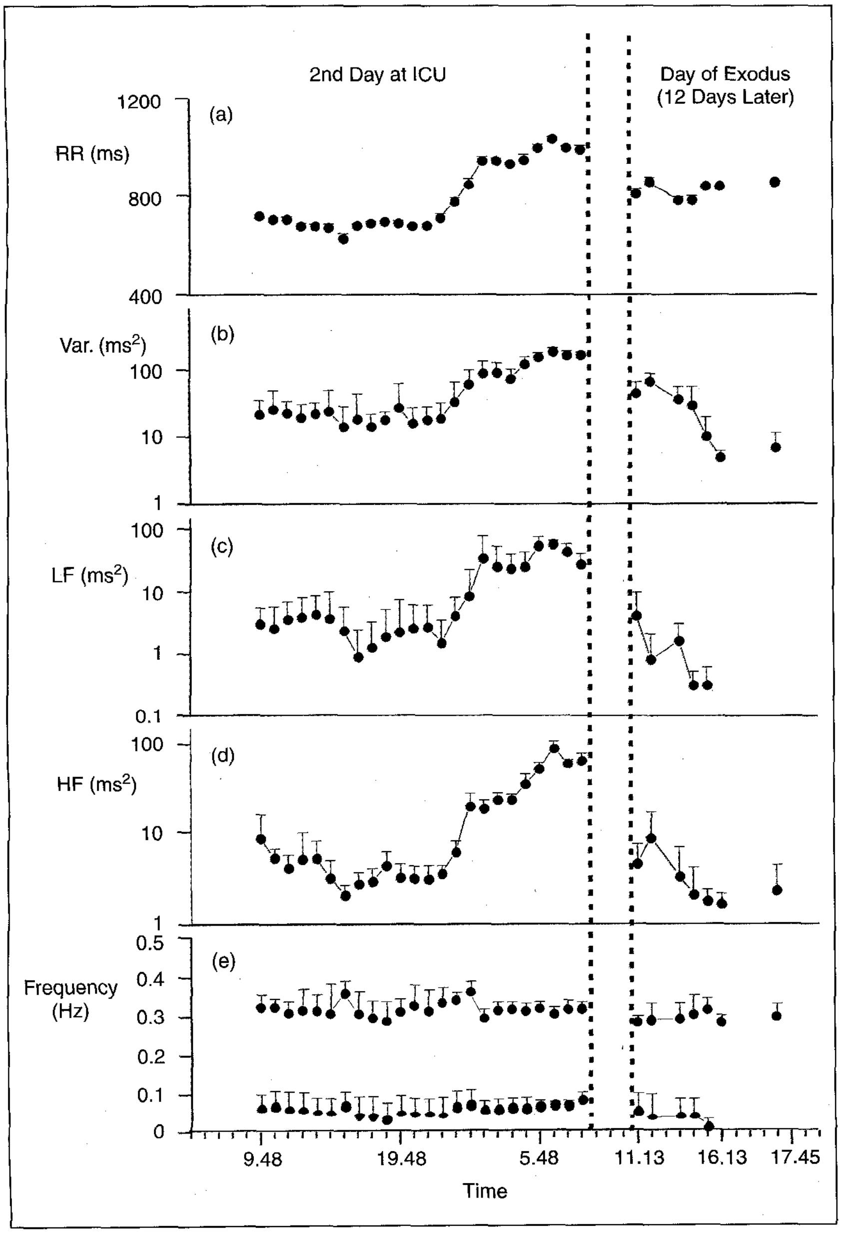
presents results obtained from particular *DL records*. The selection of the descriptive cases was done to demonstrate both the potential usefulness and the possible problems connected with the extraction of spectral parameters from ICU patients.

Short-Term Parameters

As an example, Fig. 2 shows the variability series during and after airway suctioning, beginning at sample #200. AWS produced changes in the variability series, affecting both the mean values and the oscillatory pattern of the series. In particular, mean RR interval was reduced, while mean SAP and PAP values increased. All these parameters showed a slow course of recovery toward the presuction values, which lasts up to over 1500 samples after the AWS (roughly 12 minutes in this case). RR and SAPs values showed the slower recovery trend. Several artifacts, on each beat-to-beat measure during the suction, are clearly visible in the figure, suggesting not to consider data during these epochs.

The main variability results are shown in Table 2 and Fig. 3. Suction caused changes in both RR interval and pressure values. RR interval decreased significantly (mean ± std:606.24 ± 90.65 vs 576.69 ± 72.72 ms; $p < 0.05$). During suction, the nonstationary and sometimes noisy pattern of the beat-to-beat series did not allow reliable analysis of the spectral parameters of HRV. LF power, however, was increased after suction, as compared to the basal value (14.49 ± 17.38 (basal) vs 30.2 ± 42.97 ms^2; $p < 0.05$). On the contrary, neither HF power (21.87 ± 90.63 vs 37.8 ± 122.48 ms^2; ns) or RMSSD values (7.37 ± 12.28 vs 11.51 ± 22.00 ms; ns) were increased in the same period. In the following epoch (epoch V) data returned closer to their basal values.

Systolic SAP (110 ± 18 vs 133 ± 30 mmHg; $p < 0.05$), PAP (27 ± 17 vs 37 ± 20 mmHg; $p < 0.05$) and CVP values (3 ± 5 vs 9 ± 7 mmHg; $p < 0.05$) were all increased during suctions, but only SAPs values remained at an elevated level after suction and decreased gradually thereafter. The increase during AWS affected LF, HF power, and RMSSD values. All these measures, however, were relatively noisy during epoch III, which reduces their reliability.



7. Hourly trend for the RR spectral parameters. The trends evidence the dramatic reduction in all the spectral parameters before the death of the patient

Long-Term Parameters

Examples of the 24-hour spectral pattern for RR, SAP, and PAP series are shown in Fig. 4. Data are obtained from record #27. Figure 4(a) illustrates the RR series of a subject who survived after intensive care. It shows values of the slope near 1, thus indicating a condition of normal cardiovascular regulatory mechanisms. Even the SAP and PAP spectrum analysis (Figs. 4(b) and (c)) confirm the presence of a long time correlation.

The results of the long-term analysis are summarized in Fig. 5 for the two populations. The α-slope parameter computed over the 24-hour spectrum RR interval series differed in deceased and survival patient groups (1.44 ± 0.35 vs 1.13 ± 0.10, respectively; $p < 0.05$). The slope of the SAP (1.21 ± 0.17 vs 1.27 ± 0.21; ns) and PAP time series (1.05 ± 0.25 vs 1.18 ± 0.35; ns) did not evidence differences between the two groups.

Report of Cases

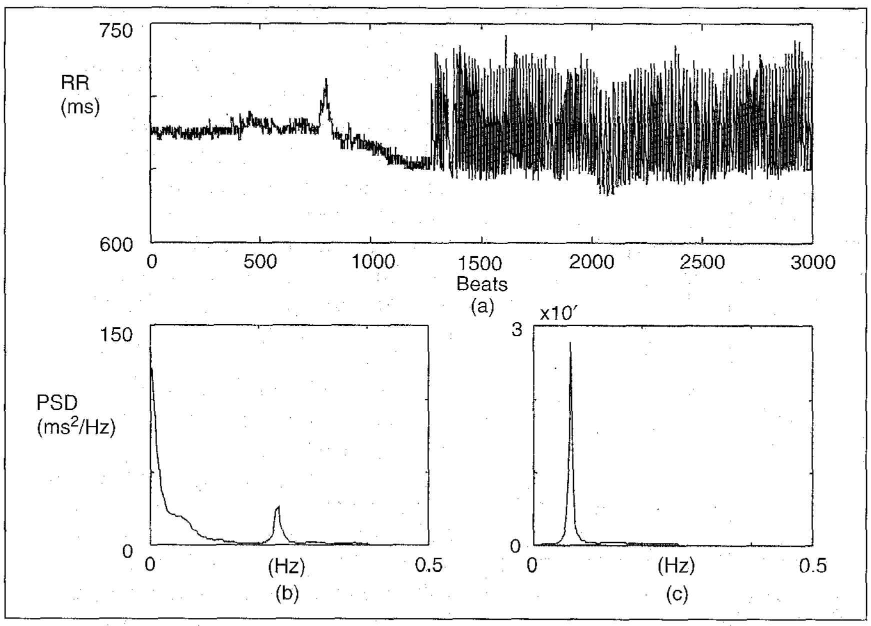
We also present specific cases in order to demonstrate possible problems in the interpretation of spectral patterns for ICU patients. Two examples will be shown: in the first, the spectral parameters are used to monitor the status of an

ICU patient, while in the second case, the influence of the external ventilator on RR interval is considered. In Fig. 6, the spectrum of RR, SAPs, and AWF series have been computed for the same patient in different epochs. Data come from various records of the DL (records #56, #59a, #59b). The first file was recorded 2 days after the patient entered the ICU; while the two successive files were registered 12 days later, within 6 hours and within 0.5 hour before the death of the patient, respectively. The spectral pattern changes considerably from the first recording (Fig. 6(a-c)) to the final (Fig. 6(g-i)). Global variance decreases in going from the upper spectra to the lower ones, affecting both LF and HF rhythms in the RR and SAPs series. In particular, the LF rhythm disappears in both RR and SAPs spectra in Fig. 6(d,e), while the residual HF modulation is induced by the external ventilator. No variability is found in the lower spectra except for the mechanical influence of the ventilator on SAPs.

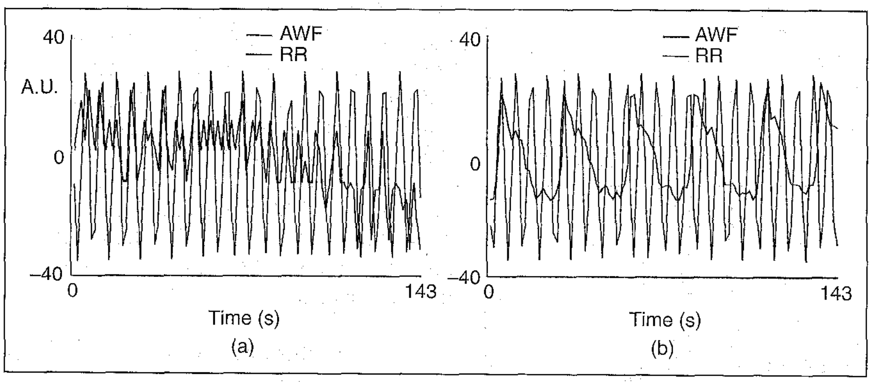
The heavy reduction in spontaneous variability is clearly evidenced in the hourly trend of spectral parameters shown in Fig. 7. Both LF and HF powers and variance show a decreasing trend in the hours preceding the death. In particular, the fall in LF rhythms seems to precede the decreasing in both total variance and HF power values. No LF rhythms are found in the 2 hours preceding the death of the patient. In Table 3, the mean hourly values in the last 6 hours of the recording are compared with the basal period. The basal period includes the first 10 hours of record #56 (see also Fig. 7 for reference). The table shows that LF power is significantly reduced just 5 hours before the death of the patient, while both HF and total variance parameters, in the same period, maintain values similar or higher than in basal conditions. A significant decrease in total variance is found two hours later, when no more LF components are detectable in the spectra.

The second example shows possible effects of mechanical ventilation on HRV. The ventilator exerts sinusoid positive pressure on the cardiovascular system, which may interfere with physiological mechanisms of control. Frequently, such an interaction could be interpreted as linear, as in the case of respiratory sinus arrhythmia quantified through spectral techniques. However, sometimes nonlinear interactions can be seen such as during entrainment [40] or coupling cycle. In order to display nonlinear interactions between mechanical ventilation and HRV, Fig. 8 shows the tachogram obtained from patient #3 of the DL. Two epochs can be clearly recognized. In the two epochs, both the signal variance and the harmonic contents of the signals are different (Fig.

Long-term parameters significantly differ between patients who survived and those who did not.



8. Tachogram obtained from record #3 of the DL. The spectral characteristics of the RR series (a) suddenly change, as shown by the different spectral patterns in (b, c). The two PSDs are obtained from the left part (b) and from the right part (c) of the tachogram, respectively.



9. Superimposition of RR interval tachogram (red line) and ventilation beat-to-beat series (black line). In (a), the mechanical ventilator modulating the RR variability induces cycling variation corresponding with each ventilatory act. In (b), the external ventilation is able to trigger a nonlinear interaction, and the RR variations are induced with a rate 1:4 respiratory acts. It may be interesting to note that a one-to-one response is still present in (b).

8(a)). In particular, while a HF rhythm *predominantly influences* the spectrum of the first part of the tachogram (Fig. 8(b)), the spectrum of second part shows a stable rhythm that falls into the LF range (Fig. 8(c)). Such a rhythm could be erroneously attributed to the common source of LF frequency oscillations, if one simply looks at the PSD of the tachogram. However, this is a rhythm that is triggered by respiration, as shown in Fig. 9(a, b). This figure was obtained by superimposing the beat-to-beat series of RR and respiration. Fig. 9(a) refers to the first part of the tachogram of Fig. 8(a), while Fig. 9(b) is obtained in correspondence with the second part of the same RR series. In the latter case, respiration induces variations in RR intervals that are synchronized every four inspirations, with the typical period-doubling pattern that characterizes nonlinear interactions [41].

Discussion and Conclusions

Only limited data are currently available on cardiovascular variability beat-to-beat series in ICU patients. We therefore analyzed both short-term and long-term variability parameters in ICU patients extracted from the IMPROVE DL. Short-term parameters, obtained from HRV, showed decreased RR interval values and an increased LF power in the five minutes following the AWS maneuver. Neither HF power nor RMSSD values increased, suggesting an increased sympathetic activity induced by AWS. Such an activation may be expected on a clinical basis. In fact, the manipulation of larynx and upper trachea with laryngoscopopy and endotracheal intubation causes a sympathoadrenal response with increase in arterial pressures and heart rate [42-43]. Similar responses are seen in ICU patients during and after AWS. Short-term parameters, obtained from SAP, did not show relevant variations, except an increase in SAP mean value and in RMSSD immediately after the suction. Similar results were found for both PAP (just a slight increase in LF power after the suction) and CVP index. Although the ANS control indexes did not change consistently, the increase is certainly relevant from a clinical point of view.

Long-term parameters significantly differ between patients who survived and those who did not. The former showed α-slope values close to 1 (almost normal values), while the latter had significantly

The correct attribution of spectral changes to the proper causes may be very complex.

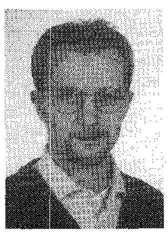
higher values. As pointed out in the methods section, spectra following the scaling law can be identified only when the α-slope value exceeds 1: the patients analyzed have RR signals with strong power-law relations. In the class of patients who survived, α assumes values higher in respect to physiologically normal subjects and more similar to the values that can be found in the analysis of HRV signal in hypertensive patients [44]. The increase of α-values in patients who died confirmed the prognostic value of the index for the evaluation of death risk. On the contrary, slope of PAP and SAP spectra did not differ between the two groups.

Results obtained for pressure variability in ICU patients seem to indicate a greater stability of these signals. Short-term and long-term indexes maintain or show only small changes with respect to normal patterns, even in nonphysiological conditions. These results indirectly confirm the RR series as a most sensitive index of altered physiological status.

The changes in short-term variability parameters during and after AWS, and previous results on HRV parameters, in ICU patients [23-25] suggest that cardiovascular variability analysis may be helpful in monitoring the ANS balance during ICU treatments and disorders. Our measures followed the end course of the patients who died. Results show a drastic reduction of all the variability parameters, which started 5 or 6 hours before the patient's death. In particular, disappearance of the LF components in both RR and SAP spectra is in agreement with previous results [23], which indicated in the depressed LF rhythm a predictor of mortality in ICU patients.

Even if variability parameters may in the future have clinical relevance for the routine monitoring of ICU patients, their interpretation presents several problems. Various factors (such as different disorders, diagnoses, and medications) might influence the RR and SAP variability. Thus, the correct attribution of spectral changes to the proper causes may be very complex. In addition, short-term variability parameters during arrhythmias, atrial fibrillation, or when cardiac contractions are ruled by a pacemaker may provide different information that must be properly interpreted. Finally, the use of mechanical ventilation for most ICU patients may heavily influence physiological variability, making it sometimes difficult to attribute changes in the spectral rhythms to sympathetic or parasympathetic activity. In the example presented, the ventilator triggered a huge rhythm in the RR interval. Such a rhythm was found to fall in the LF range as a result of nonlinear period-doubling mechanisms. This interaction may also have clinical relevance with ANS control. Despite these problems, long-term parameters were predictive of patient death even in the presence of different disorders and moderate arrhythmias during the recordings.

In conclusion, both short-term and long-term spectral parameters were employed for the assessment of patient status in the ICU. Short-term parameters were sensitive to the AWS and may also be employed to monitor the response to different therapeutic interventions. Long-term parameters showed significantly increased α-slope values in nonsurviving patients. This result suggests that the α-slope value on 24-h RR spectra may be a relevant prognostic index.



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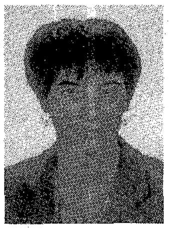

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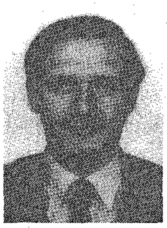

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