Heart Rate Variability as Early Marker of Multiple Organ Dysfunction Syndrome in Septic Patients

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Purpose: To determine whether measuring heart rate variability (HRV) in a group of septic patients without multiple organ dysfunction syndrome (MODS) made it possible to predict which of them would later develop this syndrome.

Material and Methods: We studied 46 septic patients without MODS at the time of admission to an intensive care unit (ICU). During the first 24 hours of admission, a 10-minute electrocardiogram (ECG) was performed and 8 HRV indexes were calculated off-line. Eleven patients later developed MODS (MODS group) during their ICU stay, and 28 did not (non-MODS group). Seven patients were excluded.

Results: Although Acute Physiological and Chronic Health Evaluation (APACHE II) scores were similar for both groups, most HRV indices on admission were reduced significantly in the MODS group. Compared with a subset from the non-MODS group (control group, n = 11) paired by age, the MODS group had significantly lower low-frequency spectral components (LF, $P = .0128$) and mean squared successive differences of R-R intervals (rMSSD) ($P = .0473$) values. Multivariable logistic regression identified LF as the best predictor of MODS and received operating characteristic (ROC) curves established its cut-off point at 18 ms^2. Mortality rates were 63.6% for the MODS group and 0% for the non-MODS group ($P < .0001$).

Conclusions: Reduction of HRV on ICU admission may be useful in identifying septic patients at risk for development of MODS.

SEPSIS IS THE LEADING cause of mortality in intensive care units (ICUs).[1]

Septic patients have better prognoses when multiple organ dysfunction syndrome (MODS) is not present.[1,2] Therefore, from a clinical point of view, the prognostic breakpoint is the appearance of MODS. Mortality rate increases from 5% to 30% to 100% when MODS is present.[2]

Surgical and drug therapies[3] have failed to reduce MODS mortality. Godin and Buchman[4] gave another point of view when they argued that although single organ recuperation is necessary, it is not sufficient per se to restore homeostasis of the entire system. MODS alters the functional relationship among organs, which could be regarded as oscillators, coupled among themselves according to nonlinear dynamics.[4-6] If the coupling is broken, the isolation of organs (referred to as *decomplexification*)[7-10] leads to systemic dysfunction. It often has been noted[4,5] that usual therapies are initiated too late, when MODS already is present, that is, when organ oscillators already are uncoupled. The performance of each organ affects the behavior of the whole body[8,11] and can be analyzed through the study of the organs' temporal patterns.[12]

Regarding the heart, the variability of the R-R interval (heart rate variability [HRV]) also depends on the coupling between the heart and other organs.[9] Reduction of HRV could represent the effect of the earlier mentioned decomplexification on the heart.[11,13,14] If so, HRV would seem to be a readily available tool for the evaluation of nonlinear dynamic relationships among organs.[6,15]

At present, medicine lacks a useful score capable of detecting septic signals before MODS develops.[16] We hypothesized that a reduction in HRV is an early marker for MODS. The main goal of our study was to determine whether HRV impairment preceded a diagnosis of MODS. To test our hypothesis we measured HRV in septic patients without MODS. Then, we prospectively followed the evolution of these patients during their ICU stay and retrospectively compared HRV indexes for the group of patients that developed MODS and the group that did not.

MATERIALS AND METHODS

The procedure used in this study was approved by the Ethics Committee of the Facultad de Medicina of Montevideo, Uruguay. We performed no

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medical interventions and our measurements did not interfere with the ICU monitoring routine. Written consent was requested from the patients themselves whenever it was possible. Otherwise family consent was solicited. We studied 46 septic patients admitted to a 24-bed ICU in a tertiary-level hospital (Hospital Pasteur, Montevideo, Uruguay). The patients included in our study was not the total number of patients admitted during the time period encompassed in our study. Instead, we chose 2 categories of patients frequently represented in our ICU: those with severe community-acquired pneumonia and those who had recently undergone abdominal surgery. The criterion for patient selection was a diagnosis of septic disease[17] without MODS (according to Marshall et al[18]) at the time of admittance into the ICU, which also was when an electrocardiogram (ECG) was performed for HRV analysis. Criteria for exclusion were: symptoms of MODS, nonsinusal rhythm, use of anticholinergic or β-blocking medication, diabetes, neuropathies or diagnosed autonomic dysfunction, congestive heart failure of functional class III to IV, or myocardial infarction (acute or previous). Patients with more than 10% nonsinusal beats also were excluded. In keeping with these criteria, 2 patients were excluded for diabetes and 5 patients were excluded for arrhythmias, reducing the initial group from 47 to 39 patients.

For each patient we prospectively recorded age, sex, previous disease and McCabe and Jackson classification,[19] central body temperature, blood pressure, heart rate, respiratory rate, $\mathrm{PaO_2/FiO_2}$, serum creatinine concentration, blood ureic nitrogen level, serum bilirubin level, leukocyte and platelet count, hematocrit level, prothrombin time, Glasgow coma scale, ventilatory mode, length of ICU stay, and ICU mortality. APACHE II scores[20] were assessed within the first 24 hours after admittance to the ICU.

HRV Analysis

Short-term ECG recordings for HRV analysis were performed within the first 24 hours of the patient's admission to the ICU. To avoid circadian-related HRV disparities, all the recordings were performed between 9 and 11 PM. All patients were studied in a supine position, for a period of 10 minutes (see Appendix for a description of the equipment used). After that, we performed an off-line analysis. At that time, we were blinded as to patient condition. A Matlab-based algorithm (The Math Works, Inc, Natick, MA) was used to detect R waves (see Appendix). The software we used also made visual validation of the entire record and correction of false positives (related to movements or extrasystolic beats) and negatives (lack of detection) possible. Thus, we obtained very reliable data. Another software program, written in Matlab base, was used to measure R-R intervals and calculate HRV indexes.

Among the different indices available to us, we chose several from different domains (see Appendix). In the time domain, we calculated the standard deviation of R-R intervals (SDNN) and the square root of the mean squared successive differences of R-R intervals (rMSSD). In the geometric domain we used the triangular interpolation of R-R intervals (TINN), obtained as the baseline width of the minimum square difference triangular interpolation of the highest peak of the histogram of R-R intervals. In the frequency domain we calculated heart rate power in the low-frequency range (0.04-0.15 Hz) (LF), and in the high-frequency range (0.15-0.40 Hz) (HF) in absolute and normalized units (LF or HF/[LF + HF] × 100). This was performed by Welch's method of power spectral density estimation (see Appendix). The ratio of LF/HF also was obtained.

MODS and Non-MODS Populations

The diagnosis of MODS was based on the score defined by Marshall et al[18]: MODS was diagnosed when 2 or more dysfunctions were present for at least 24 hours. Organ failure was defined as a score greater than 2 in a given system.

Among the 39 patients studied, 11 developed MODS during the 40 ± 29 hours (mean ± SD) after the ECG recording; these patients are referred to as the MODS group. The remaining 28 patients did not develop MODS during their stay in the ICU and are referred to as the non-MODS group. When we compared age, heart rate, sex, APACHE II score, and previous disease for both groups (see Table 1), the only significant difference we found was in mean age (the non-MODS group was younger than the MODS group). Because age is one of the most powerful determinants of HRV,[21,22] we chose a subset within the non-MODS group comprising the 11 oldest patients. It is important to stress that the researcher who selected these 11 patients was blinded to the results of the

Table 1. Main Characteristics of the MODS and Non-MODS Groups

	MODS Group (n = 11)	Non-MODS Group (n = 28)
Age (years)*	59.5 ± 17.8	39.6 ± 19.5
Heart rate (bpm)	103.2 ± 20.5	93.3 ± 16.4
Gender (n) male/female	5/6	19/9
APACHE II Score	15.5 ± 6.7	13.6 ± 6.3
Previous disease[†] n (%)		
Rapidly fatal	0	0
Ultimately fatal	2 (18.2)	6 (21.4)
Nonfatal	9 (81.8)	22 (78.6)

NOTE. Values are given as mean ± SD of all the data or as number of patients (n) and %.

*Age is the only variable that shows significant differences between groups ($P = .0066$)

[†] McCabe and Jackson Classification.[19]

HRV analysis performed at the time of admittance. This subset of the non-MODS group is referred to as the control group. When we compared the variables listed in Table 1 for the MODS group and the control group there were no differences between them, even regarding age (see Table 2).

Statistical Analysis

Variables were analyzed comparing mean values by using the Mann Whitney test (GraphPad Instat Version 3.01; GraphPad Software, San Diego, CA). For comparing proportions, the Fisher exact test was used. A 2-tailed P value of less than .05 was considered statistically significant, in such a case, exact P values are given. Nonsignificant values are labeled NS. Results are given as mean ± SD of all the data.

An exact, nonparametric, multiple logistic regression[23] was performed to analyze the risk for developing MODS (dependent variable) as a function of the relevant covariates (LogXact 4, Sytel Software Corporation, Cambridge, MA). The independent variables incorporated were age, APACHE II score, and the HRV indices (SDNN, rMSSD, TINN, LF, and HF).

To find the best index for predicting MODS, we calculated the nonparametric receiver operating characteristics (ROC) curves. Area under the curves, specificity, sensibility, and cut-off points were considered (Epidat 2.1; Pan American Health Organization, Washington, DC).

RESULTS

At the time of ECG recording for HRV analysis, the clinical and laboratory parameters listed in the Materials and Methods section did not show statistically significant differences for the MODS and non-MODS groups. Seven patients received inotropic drugs, either dopamine or dobutamine. In the MODS group, 4 patients received dopamine (the doses were in μg/kg/min of 3, 5, 5, and 8); and 1 patient received dobutamine (5 μg/kg/min). In the non-MODS group, 1 patient received dopamine (5 μg/kg/min) and another received dobutamine at the same dose. There were no statistically significant differences either in number of patients treated with inotropic drugs or in the doses of such drugs. The number of patients receiving invasive mechanical ventilation, in all cases synchronized intermittent mandatory ventilation, was 7 in the MODS group and 8 in the non-MODS group. Additionally, 4 patients in the MODS group and 20 in the non-MODS group had spontaneous ventilation (either with an oxygen mask or without any support). A Fisher exact test did not show differences in respiratory support between groups.

Among the 39 patients, 7 died during their ICU stay (17.9%). All of them belonged to the MODS group. Therefore, the mortality rate of this group was 63.6% (7 of 11). The non-MODS group had a 0% mortality rate at the time of discharge from the ICU ($P < .0001$). Because the patients in the control group were selected from the non-MODS group, their mortality was also 0% ($P = .0039$).

HRV Analysis

Table 3 shows the mean values of HRV indexes for all the patients in the MODS and non-MODS groups. Most values are significantly lower for the MODS group. The LF/HF ratio and normalized

Table 2. Case-control Study. Main Characteristics of the MODS and Control Groups

	MODS Group (n = 11)	CONTROL Group (n = 11)
Age (years)	59.5 ± 17.8	60.0 ± 10.4
Heart rate (bpm)	103.2 ± 20.5	88.5 ± 11.4
Gender (n) male/female	5/6	9/2
APACHE II Score	15.5 ± 6.7	13.0 ± 6.3
Previous disease* n (%)		
Rapidly fatal	0	0
Ultimately fatal	2 (18.2)	2 (18.2)
Nonfatal	9 (81.8)	9 (81.8)

NOTE. Values are given as mean ± SD of all the data or as number of patients (n) and %. There are no statistically significant differences between groups.

*McCabe and Jackson Classification.[19]

Table 3. Comparison of HRV Measures for the MODS and the Non-MODS Groups

	MODS Group n = 11	Non-MODS Group n = 28	*P*
SDNN (ms)	12.8 ± 8.9	22.4 ± 15.8	.0326
RMSSD (ms)	5.5 ± 3.6	13.1 ± 12.4	.0070
TINN (ms)	49.2 ± 33.5	98.3 ± 72.1	.0218
LF (ms^2)	11.3 ± 16.3	197.0 ± 418.0	.0007
HF (ms^2)	14.8 ± 21.7	90.8 ± 226.0	.0101
LF/HF	2.3 ± 3.1	3.1 ± 2.2	ns
LFn (nu)	51.7 ± 23.7	67.9 ± 16.2	ns
HFn (nu)	48.3 ± 23.7	32.2 ± 16.2	ns

NOTE. Values are given as mean ± SD of all the data.
Abbreviation: nu, normalized units (see Appendix).

values of LF and HF were not significantly different for these 2 groups.

Table 4 shows the HRV indexes for the MODS and the control groups. Comparison between these groups yielded no significant *P* values, except for LF and rMSSD. These 2 indices were significantly lower in the MODS group.

In Figure 1 we include the tachogram, histogram, and spectral analysis obtained from 2 different patients, one from the control group (Figs. 1A-1C) and another from the MODS group (Figs. 1D-1F).

The multivariate logistic regression analysis showed that LF made a significantly greater independent contribution than the other HRV indices to the discriminatory ability of the model. Several models were calculated independently including age plus the other HRV indexes but LF was the best predictor for MODS. The logistic regression equation was MODS $= -0.044 \times$ LF -1.906 (2-sided *P* value for coefficient: $P = .003$).

Figure 2 shows the ROC curves for the 2 HRV indexes (rMSSD and LF) that differentiated the MODS group from the control group.

DISCUSSION

Because the prognosis of patients with MODS differs markedly from that of patients with a self-limiting pathology, early differentiation of these groups is clinically relevant. To date, no clinical tools have been developed for such a purpose. According to our findings, early identification of septic patients likely to develop MODS could be accomplished by means of a short-term HRV analysis. In our study, HRV impairment was present in those patients who later developed MODS although their clinical condition, at the time of admittance and ECG recording, was in other respects comparable with that of the control patients (Table 2). Specifically, the MODS group exhibited lower LF and rMSSD values, which therefore may be good markers to predict which patients subsequently will develop MODS.

Both sepsis and MODS are characterized by a complex network of mediators and toxins[24] that might influence cardiovascular reflexes, leading to an impairment of autonomic balance.[25,26] According to Kuster et al,[27] an increase in plasma cytokine levels can be observed 48 hours before the onset of neonatal sepsis. The increase in cytokines affects the autonomic nervous system (ANS).[28-30] Therefore, it is not surprising that HRV impairment should precede the onset of the changes in the clinical variables that define MODS.

The heart rate spectral analysis, which allows us to differentiate between branches of the ANS,[31] seems to be the best method for HRV assessment in critically ill patients.[32] LF components have been identified with both branches of the ANS.[33] Nevertheless, it has been noted that in critically ill patients (ie, in stressful conditions in which parasympathetic activity is diminished), LF has a stronger correlation with the sympathetic branch.[8,28]

In fact, it is precisely modulation of the sympathetic branch of the ANS that appears to be impaired in severe illness. Goldstein et al[34] have reported a reduction in sympathetic modulation in their study of experimental septic shock in rabbits. Garrard et al[31] have found that septic patients show a significant reduction in LF components. They also noted a strong positive correlation between LF reduction and ICU mortality. Piepoli et al[35] have stated that restoration of sympathetic modulation, as measured through LF behavior, is associated

Table 4. Comparison of HRV Measures in the Case-control Study

	MODS group n = 11	CONTROL group n = 11	*P*
SDNN (ms)	12.8 ± 8.9	20.7 ± 12.9	ns
RMSSD (ms)	5.5 ± 3.6	11.4 ± 7.6	.0473
TINN (ms)	49.2 ± 33.5	88.2 ± 63.2	ns
LF (ms^2)	11.3 ± 16.3	108.8 ± 199.5	.0128
HF (ms^2)	14.8 ± 21.7	43.7 ± 72.4	ns
LF/HF	2.3 ± 3.1	2.9 ± 1.9	ns
LFn (nu)	51.7 ± 23.7	68.8 ± 13.2	ns
HFn (nu)	48.3 ± 23.7	31.2 ± 13.2	ns

NOTE. Values are given as mean ± SD of all the data. Abbreviation: nu, normalized units (see Appendix).

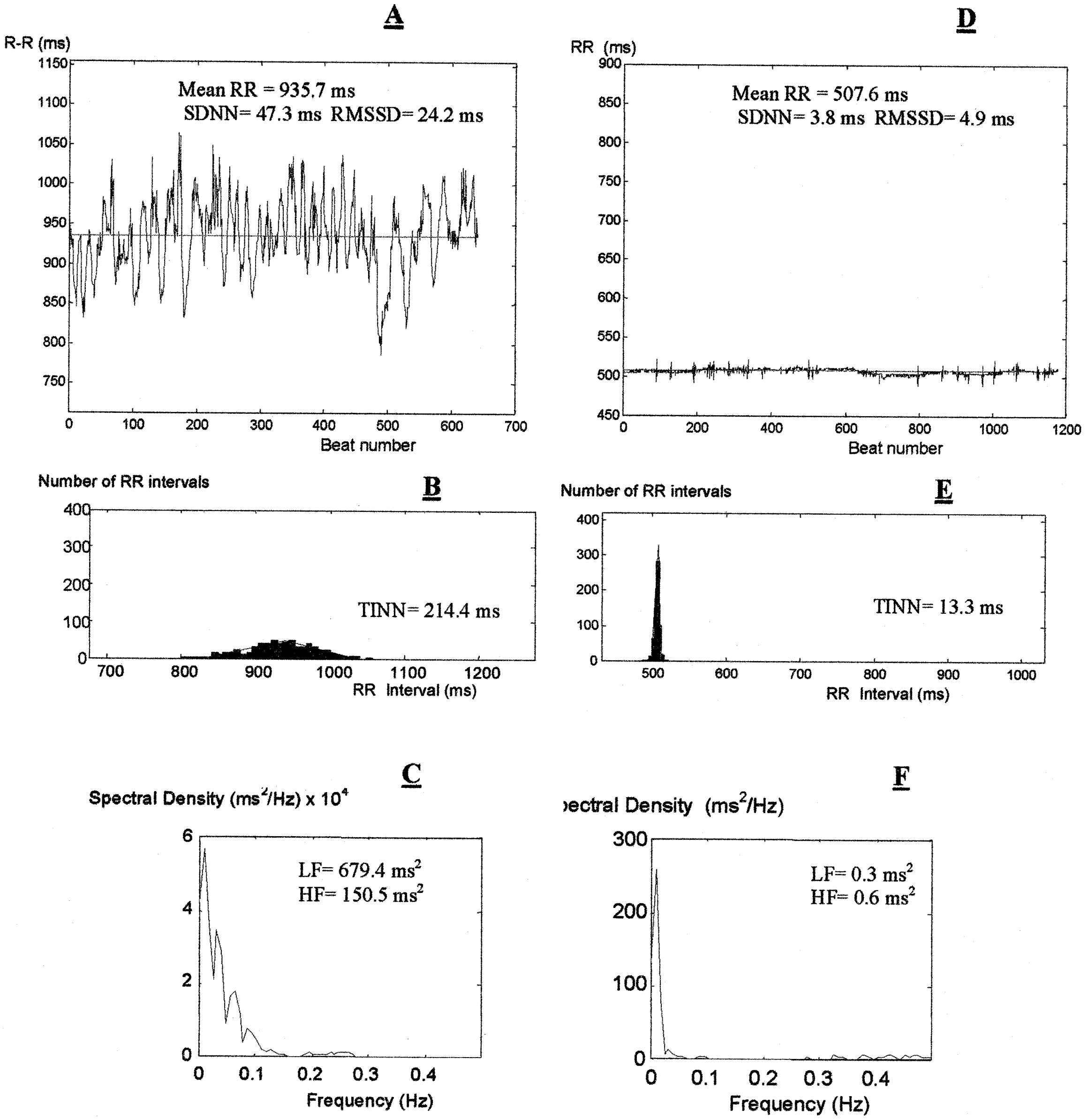

Fig 1. Example of HRV analysis in 2 patients. The ECG recordings were made during the first 24 hours after admission to the ICU. At the time of recording, none of the patients had developed MODS. (A, D) Tachograms, (B, E) the frequency histograms, and (C, F) the spectral analysis. (A, B, C) The results for patient 1 are shown, and (D, E, F) for patient 2. Patient 1 had a favorable outcome (ICU discharge on day 5 after admission). Patient 2 developed MODS 36 hours after admission and died on day 12. Although the severity scores for both patients were similar on admission to the ICU, there were clear differences in HRV. Note spectral density values × 10^4 for patient 1.

with a good prognosis in patients with septic shock. All these findings concur with ours regarding reduction of the LF band in patients who subsequently will develop MODS.

Judging by our comparisons of HRV between groups, multivariable regression, and ROC curves, of all the indices included in our study, the LF band is the most reliable indicator of impaired HRV. Given that the cut-off point for LF is 18 ms^2, we can expect to find LF values of 18 ms^2 or less in patients who will develop MODS during their ICU stay and higher LF values in patients who will not. Similar findings were reported recently for sudden cardiac death in chronic heart failure patients.[36]

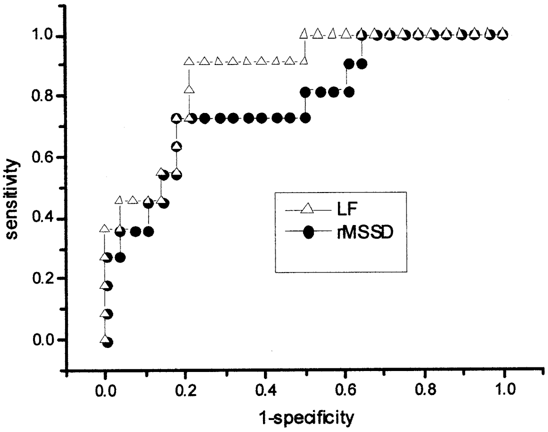

Fig 2. ROC curves for 2 HRV indexes: LF and rMSSD. The area under the ROC curve was 0.87 for LF (95% confidence interval, 0.75-0.98) and 0.78 for rMSSD (95% confidence interval, 0.62-0.95). The cut-off point for LF was 18 ms^2 (79% specificity, 91% sensitivity), and for rMSSD was 5.5 ms (82% specificity, 73% sensitivity). △, LF; ○, rMSSD.

The HF band may be used as a measure of parasympathetically mediated respiratory sinus arrhythmia in adult humans[37]; therefore, it follows that patients with mechanical ventilation could have modified HF values. However, the respiratory support that we used was a synchronized intermittent mandatory ventilation mode. By using this mode, the patients' respiratory rate always was higher than the mandatory frequency. Therefore, in our patients mechanical ventilation did not have any discernible effect on the HF components of HRV.

Limitations of our Study

The exclusion of patients with arrhythmia may turn out to have some implications regarding the usefulness of our analysis for clinicians working in the ICU. However, in our study, only 5 patients in 46 were excluded for this reason.

CONCLUSIONS

In an otherwise similar group of patients suffering from sepsis, a reduced HRV may allow us to single out those who are at risk for developing MODS before the clinical signs become evident. We therefore propose that HRV analysis and especially LF index be used as a predictor of MODS. This noninvasive method, which is both quick and easy, may well improve the prognosis of MODS patients by identifying them at a time when they are most likely to benefit from therapy.

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REFERENCES

1. Baue AE: Systemic inflammatory response syndrome (SIRS). Multiple organ dysfunction syndrome (MODS), multiple organ failure (MOF): Are we winning the battle? Shock 2:79-89, 1998

2. Medina J, Pontet J, Curbelo A, et al: Relaparotomía en sepsis peritoneal. Medicina Intensiva 2:53-61, 2001

3. McCloskey RV, Straube RC, Sanders C, et al: Treatment of septic shock with human monoclonal antibody HA-1: A randomized, double-blind, placebo-controlled trial. Ann Intern Med 121:1-5, 1994

4. Godin P, Buchman T: Uncoupling of biological oscillators: A complementary hypothesis concerning the pathogenesis of multiple organ dysfunction syndrome. Crit Care Med 7:1107-1118, 1996

5. Godin P, Fleisher L, Eidsath A: Experimental human endotoxemia increases cardiac regularity: Results from a prospective, randomized, crossover trial. Crit Care Med 24:1117-1124, 1996

6. Toweill D, Goldstein B: Linear and nonlinear dynamics and the pathophysiology of shock. New Horizons 6:155-168, 1998

7. Goldberger AL: Applications of chaos to physiology and medicine, in Kim JSJH (ed): Applied Chaos. New York, John Wiley & Sons, 1992

8. Goldstein B, Fiser DH, Kelly MM, et al: Decomplexification in critical illness and injury: Relationship between heart rate variability, severity of illness and outcome. Crit Care Med 2:352-357, 1998

9. Ellenby M, McNames J, Lai S, et al: Uncoupling and recoupling of autonomic regulation of the heart beat in pediatric septic shock. Shock 4:274-277, 2001

10. Marshall J: Complexity, chaos and incomprehensibility: Parsing the biology of critical illness. Editorial comment. Crit Care Med 7:2193-2200, 2000

11. Seely A, Christou N: Multiple organ dysfunction syndrome: Exploring the paradigm of complex nonlinear systems. Crit Care Med 7:2193-2200, 2000

12. Glass L, Mackey MC: The rhythms of life, in Ip PU (ed): From Clock to Chaos. New Jersey, Princeton University Press, 1988, pp 33-47

13. Kleiger R, Stein P, Bosner M, et al: Time-domain measurements of heart rate variability, in Malik ACM (ed): Heart Rate Variability. New York, Futura Publishing Company, 1996, pp 33-47

14. Pincus SM: Greater signal regularity may indicate increased system isolation. Math Biosci 122:161-181, 1994

15. Kennedy H: Heart rate variability: A potential, noninvasive prognostic index in the critically ill patient. Crit Care Med 2:213-214, 1998

16. Knaus W: Letters to the editor. Mortality risk prediction in sepsis. Crit Care Med 10:1793-1794, 1998

17. American College of Chest Physicians and Society of Critical Care Med Consensus Conference: Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. Crit Care Med 20:864-874, 1992

18. Marshall J, Cook D, Christou N, et al: Multiple organ dysfunction score: A reliable descriptor of a complex clinical outcome. Crit Care Med 7:1638-1652, 1995

19. McCabe WA, Jackson GG: Gram negative bacteriemia: I. Etiology and ecology. Arch Intern Med 110:847-855, 1962

20. Knaus WA, Draper EA, Wagner DP, et al: APACHE II: A severity of illness classification system. Crit Care Med 13: 818-829, 1985

21. Tsuji H, Venditti FJ, Manders E, et al: Determinants of heart rate variability. J Am Coll Cardiol 28:1539-1546, 1996

22. Migliaro E, Contreras P, Bech S, et al: Relative influence of age, resting heart rate and sedentary life-style in short-term analysis of heart rate variability. Braz J Med Biol Res 34:493-500, 2001

23. Metha CR, Patel NR, Pralay S: Efficient Monte Carlo methods for conditional logistic regression. J Am Stat Assoc 449:99-108, 2000

24. Muller-Werdan U, Werdan K: Septic cardiomyopathy. Curr Opin Crit Care 5:415-420, 1999

25. Borovikova LV, Ivanova S, Zhang M, et al: Vagus nerve stimulation attenuates the systemic inflammatory response to endotoxin. Nature 6785:458-462, 2000

26. Goldstein B: On the importance of sympathovagal balance. Crit Care Med 7:1483-1484, 2001

27. Kuster H, Weiss M, Willeitner AE, et al: Interleukin-1 receptor antagonist and interleukin-6 for early diagnosis of neonatal sepsis 2 days before clinical manifestation. Lancet 352:1271-1277, 1998

28. Toweill D, Sonnenthal K, Kimberly B, et al: Linear and nonlinear analysis of hemodynamic signals during sepsis and septic shock. Crit Care Med 6:2051-2057, 2000

29. Szabo C, Mitchell JA, Thiemermann C, et al: Nitric oxide-mediated hyporeactivity to noradrenaline precedes the induction of nitric oxid synthase in endotoxin shock. Br J Pharmacol 108:786-792, 1993

30. Griffin MP, Moorman JR: Toward the early diagnosis of neonatal sepsis and sepsis-like illness using novel heart rate analysis. Pediatrics 1:97-104, 2001

31. Garrard C, Kontoyannis D, Piepol M: Spectral analysis of heart rate variability in the sepsis syndrome. Clin Auton Res 1:5-13, 1993

32. Winchell R, Hoyt D: Spectral analysis of heart rate variability in the ICU: A measure of autonomic function. J Surg Res 63:11-16, 1996

33. Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology: Heart rate variability. Standards of measurement, physiological interpretation and clinical use. Circulation 93:1043-1065, 1996

34. Goldstein B, Fiser D, Kelly M, et al: Autonomic modulation of heart rate variability during endotoxin shock in rabbits. Crit Care Med 23:1694-1702, 1995

35. Piepoli M, Garrard C, Kontoyannis D, et al: Autonomic control of the heart and peripheral vessels in humkan septic shock. Intensive Care Med 21:112-119, 1995

36. La Rovere M, Pinna G, Maestri R, et al: Short-term heart rate variability strongly predicts sudden cardiac death in chronic heart failure patients. Circulation 107:565-570, 2003

37. Goldstein B, Buchman TG: Heart rate variability in intensive care. J Intensive Care Med 13:252-265, 1998

38. von Neumann J, Kent RH, Bellinson RH, et al: The mean square successive difference. Ann Math Stat 12:153-162, 1941

39. Malik M: Geometrical methods for heart rate variability assessment, in Malik M, Camm AJ (eds): Heart Rate Variability. Armonk, NY, Futura Publishing Company Inc., 1995, pp 47-61

40. Stoica P, Moses R: Introduction to Spectral Analysis. Upper Saddle River, NJ, Prentice-Hall Inc, 1997

41. Welch P: The use of fast Fourier transform for the estimation of power spectra: A method based on time averaging over short, modified periodograms. IEEE Trans Audio Electroacoustics 15:70-73, 1967

APPENDIX

MAIN FEATURES OF THE HARDWARE AND SOFTWARE USED TO OBTAIN ECG SIGNALS AND TO MEASURE R-R INTERVALS AND HRV INDEXES

We acquired our ECG data from the equipment used to monitor the patients in the ICU (Solar 7000-8000 version 5-D GE, Marquette; General Electric Medical System, Milwaukee, WI). Output signals were passed through an A/D converter (DAQ Card-1200 National Instruments Corporation, Austin, TX), which digitized the ECG signals; these were subsequently stored in a notebook (Compaq Armada 1130; Hewlett-Packard Company, Palo Alto, CA).

LabView-based software (National Instruments Corporation) allowed for visual checking during acquisition. The sampling rate was 500 or 1000 Hz, these differences did not affect our measurements (see later). After that, Matlab-based software made the off-line recognition of R waves possible. Detection of R waves was performed in 2 steps: (1) an automatic (by software) predetection, and (2) a manual inspection of each event performed by an expert.

The ECG signal was prefiltered to remove high-frequency noise and low-frequency baseline drift. This was performed through a Butterworth fourth-order band-pass filter with 0.3- to 25-Hz passband. A filtered ECG signal named x(t) was obtained. The predetection recognized the occurrence of an R wave combining filtered ECG level and slope (ie, when $x(t) > \text{thershold1}$ and $dx(t)/dt > \text{threshold2}$, an event is recognized, and the R wave occurrence is assigned to the maximum of the ECG signal).

Then we used a manual-revision program, written using LabView. Such visual inspection enabled us to identify false detections (both negative and positive) and make any necessary corrections.

Whenever a false positive related to an artifact was detected, the researcher manually deleted the spurious hit. Because only sinusal beats must be considered in HRV calculations, any nonsinusal beats had to be removed. In these cases, a new hit was placed obtaining 2 new intervals with a duration ± 20% of the average of the last 3 R-R intervals.

In the case of false negatives, new hits were added. The position of the new hits were determined either by a nondetected R wave or through calculation, based on the length of the previous intervals.

As a result of this inspection, we obtained an R-R sequence that was highly representative of the sinusal rhythm of the patient. Nevertheless, the record was discarded if the number of manual changes was higher than 10% of the total number of intervals.

Later, the duration of the R-R intervals was measured by means of software written in Matlab. Finally, HRV indexes were calculated using another Matlab-based program.

The rationale for choosing the HRV indices used in this study was:

Time domain: SDNN and rMSSD. SDNN is the first approach to HRV analysis and it is used widely in many publications. rMSSD is a good estimator of short-term variability.[38] Although SDNN does not take into account the order of intervals, rMSSD evaluates the differences between adjacent intervals.

Geometric domain: The histogram of intervals and its measurement by TINN is a useful index that is easy to understand. It is a modification of the triangular index, but less dependent on sampling rate.[39]

Frequency domain: It generally is agreed that power spectral analysis is one of the most useful for management of HRV data. That is especially true for short-term studies. Spectral analysis was performed estimating the power spectral density using a classic technique: the Welch's method,[40,41] which yields smoother curves than those generated by the more widely used fast Fourier transform. The R-R sequence was interpolated with a cubic spline and uniformly resampled ($Fs = 4$ Hz). The parameters used in the Welch's method were: 4 nonoverlapping segments using a Hanning window, and 256 frequency points for spectral estimation between 0 and Fs/2.

COMMENTARY

Probing Chaos in Search of Health

Michael R. Pinsky

IN THIS ISSUE of the *Journal of Critical Care*, Pontet et al[1] use analysis of heart rate variability (HRV) to assess whole-body wellness in a nonspecific group of critically ill patients. Patients were stratified post hoc into those who develop multiple organ dysfunction syndrome, and those that do not. The authors showed that on day 1 the multiple organ dysfunction group displayed no HRV, whereas the other group did. The implications of this study are that HRV reflects loss of autonomic integration or that some overriding influence eliminated the common HRV seen in patients. Because HRV can be measured easily noninvasively using a simple electrocardiographic signal, the implications of these data are significant. However, before one goes off examining HRV in all patients, it is relevant to understand the foundations to this approach, its limitations, and further applications. HRV is merely the single output measure of the complex system described by chaos theory. Chaotic behavior is not random behavior. Its application to medicine forms the very basis of our mathematic understanding of complex systems,[2] such as autonomic control[3] and innate immunity.[4] Presently, powerful but deceivingly simplistic new tools have been developed to take

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