4

Linear and nonlinear analyses of respiratory patterns in preoperative evaluation

J.J. Dronkers
C.J. Dronkers
N.L.U. van Meeteren
A. Daffertshofer

Submitted for publication

ABSTRACT

Introduction: The adaptive capacity of the respiratory system is of vital importance to cope with its functional decline after major abdominal and thoracic surgery and to prevent postoperative pulmonary complications. In this feasibility study we investigated the discriminatory properties of linear (variability) and nonlinear (entropy) analyses of the respiratory pattern in the assessment of the adaptive capacity of the respiratory system for use in the preoperative stratification and by use of a short-term sample time (3–5 minutes).

Methods: Six young healthy volunteers (controls: 2 female/4 male; age 24±4 years) and 10 persons indicated as high-risk for postoperative pulmonary complications (patients: 4 female/6 male; 71±13 years) were included. All subjects performed a respiratory test covering 70 eupneic breathing cycles. Variability of the pressure curve was quantified by the coefficient of variation (CV) of the inter-breath intervals and the amplitudes. Complexity was determined as sample entropy (SE). Differences between the groups were analyzed by the Mann Whitney U test.

Results: The median CV of the inter-breath intervals was 0.11 (IR 0.09–0.15) for controls and 0.10 (IR 0.07–0.13) for patients (p=0.45). The median CV of the amplitudes of the inspiratory curves was 0.19 (IQR 0.13–0.22) and 0.13 (IR 0.09–0.20) for controls and patients, respectively (p=0.19). For the expiratory curves the median was 0.22 (IR 0.13–0.31) for controls and 0.12 (IR 0.07–0.22) for patients (p=0.16). The median SE was 0.29 (IQR 0.22–0.43) for controls and 0.19 (IR 0.14–0.24) for patients (p=0.03).

Conclusion: We demonstrated the feasibility of linear and nonlinear measures in the preoperative assessment of the adaptive capacity of the respiratory system. Sample entropy significantly distinguished young/healthy persons from persons at high risk for postoperative pulmonary complications after major abdominal and thoracic surgery.

INTRODUCTION

General surgery stresses the human physiological system. Major abdominal and thoracic surgery induce a sharp postoperative decrease in respiratory function putting patients at risk to develop postoperative pulmonary complications (PPCs),[1] especially in frail patients. PPCs are the leading causes of postoperative morbidity and mortality and increase hospital length of stay, medical consumption and, hence, costs in patients after major abdominal and thoracic surgery.[2-4] Screening and training of the respiratory muscle function is increasingly part of the preoperative care in abdominal and thoracic surgery.[5-8] It aims for evaluating and optimizing the adaptive capacity of the respiratory system.

At present, the respiratory function and its adaptive capacity are assessed by the mere strength and endurance of the inspiratory muscles. Here we advocate a supplementary approach to relate adaptive capacity with the variability and other dynamical characteristics of respiratory signals. The breathing pattern is not a strictly periodic movement but arises from stochastic, nonlinear biological mechanisms interacting with a fluctuating environment[9] and display seemingly erratic variations in frequency and shape. These variations may be quantified by conventional statistics, e.g., the variance breath-to-breath intervals and amplitudes of the respiratory pattern. This approach primarily addresses the randomness or stochasticity of the observed variations and implies that the generating (physiological) process is linear, at least by good approximation. Alternative measures may explicitly speak to the nonlinear dynamics underlying the observed variation, which may indeed stem from interactions between many participating components of the process under study.[10] The variations are thus not merely erratic but may show so-called complex characteristics, to think of long-term correlations, 1/f spectral distributions, and so on. These characteristics are often considered to depend on age[11-13] (rigid and little fluctuations in the variable under study) and, e.g., the presence of disease[14-16] (large fluctuations and loss of control). In both cases one can observe effects on the adaptive capacity of the physiological system.

Most studies studying the variability of respiratory signals built on reasonably long recording times.[17,18] providing the opportunity to investigate a huge arsenal of complexity-related measures. Our focus on preoperative assessments of the adaptive capacity of the respiratory system, however, demands to consider short recording times, which hampers many quantitative approaches such as fractal dimensions and scaling properties. We here used entropy as an appropriate measure,[19] it appears particularly robust when considering data sets containing brief signals.

To assess the adaptive capacity of the respiratory system by use of linear and nonlinear analyses in preoperative clinical practice, we posed the following research question: what is the feasibility of a brief sample protocol (3–5 minutes) in determining the difference of variability and entropy of the respiratory pattern between young healthy adults and older patients who are known to be at risk for a postoperative pulmonary complication after major abdominal and thoracic surgery?

METHODS

Subjects

Six male and four female patients representing the so-called the high-risk group were included in this exploratory observational study (mean age: 71 ± 13 years). They were all at high risk for postoperative pulmonary complications after abdominal or thoracic surgery, i.e. met at least one of two risk factors: age >65 years and COPD.20-22 Seven of them were aged 65 years or older and six of them were diagnosed with COPD. Three patients met both conditions. In additional we included six young and healthy volunteers as a control group (four males and two females; mean age: 24 ± 4 years).

Patients were under treatment at the department of physiotherapy (Gelderse Vallei hospital). The controls were recruited among university students and employees of the hospital. All subjects were asked for informed consent for participation in the study. The local Medical Ethics Committee of the Gelderse Vallei Hospital approved the study protocol.

Procedure & measurement

Respiratory signals were obtained by use of the Respiratory Muscle Analyzer (MicroRMA /Micro Medical Limited, Rochester, UK). This device continuously registers mouth pressure at a sampling rate of 10 Hz. The resistance of the device was preset to zero by the investigator and patients were instructed to breath normally because eupneic breathing is considered the optimal presentation of adaptive capacity.[23] The test covered 70 breathing cycles (i.e. approx. 300 sec.; corrected for breaks during the test).

Data analysis

Visual inspection of the respiratory signals readily revealed a qualitative difference in signal variations between the patients and controls. We illustrate this in Figure 4.1 showing the respiration curves of a representative control (Figure 4.1A) vis-à-vis a patient at high risk for a postoperative pulmonary complication (Figure 4.1B). Both curves cover a period of 22 seconds in the second minute of the test.

We quantified outcome measures data using Matlab® (version 2011b; Mathworks Inc. Natwick, MA). Variability of the respiratory signals was determined as the coefficient of variation of the inter-breath intervals, i.e. distances between maximums of the inspiratory pressure curve and the coefficient of variation of the inspiratory and expiratory amplitude of the pressure curves. The entropy was estimated via the sample entropy (SE).[19] In brief, sample entropy represents the negative natural logarithm of the conditional probability that two sequences similar for *M* points remain similar at the next point with tolerance *r*. The *r*-value was set on 0.15 based on analysis by Lake.[24]

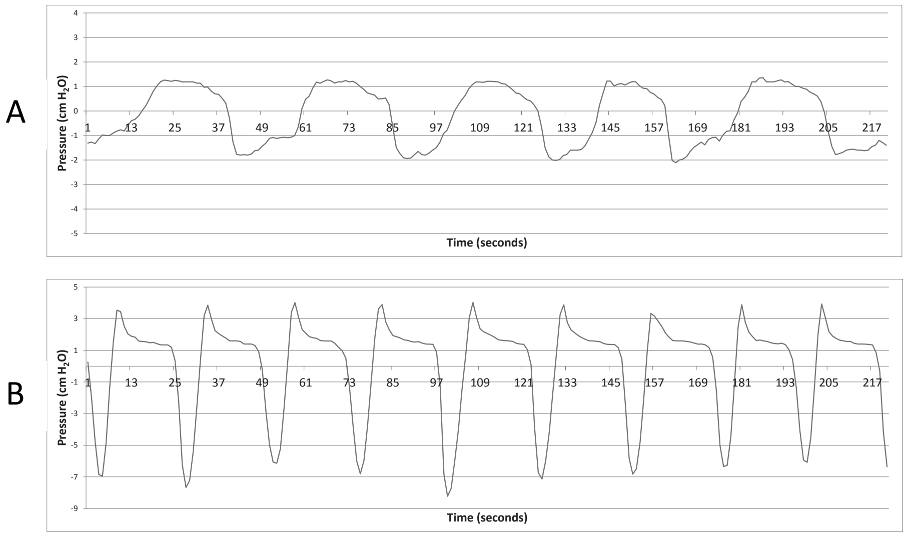

Figure 4.1 Breathing pattern of a young healthy volunteer **(A)** and a patient at risk for a postoperative pulmonary complication **(B)** during the second minute of the recording.

Statistics

SPSS Statistics (version 19.0, SPSS Inc., Chicago, IL) served for the statistical analysis. Characteristics of study participants were summarized using means and standard deviations in case of continuous variables or frequency and percentage distributions in case of categorical variables. Coefficients of variations (CV) of inter-breath intervals, amplitudes of the pressure curves and sample entropy (SE) were expressed as median and interquartile range (IR). Differences in coefficients of variation between the two groups were estimated with a non-parametric independent sample t-test (Mann-Whitney U-test). Correlations between the linear and nonlinear measures were computed using Spearman's rank correlation.

RESULTS

All subjects completed the test successfully. The breathing frequency was 15.4 (± 1.8) and 18.6 (± 4.5) breaths per minute for the control and patient group, respectively.

The median CV of the inter-breath intervals was 0.11 (IR 0.09–0.15) for controls and 0.10 (IR 0.07–0.13) for the patients (Mann Whitney U test; p=0.45). The median CV of the amplitudes of the inspiratory curves were 0.19 (IR 0.13–0.22) and 0.13 (IR 0.09–0.20) for controls and patients, respectively (Mann Whitney U test; p=0.19). For the expiratory curves the median CV was 0.22 (IR 0.13–0.31) for controls and 0.12 (IR 0.07–0.22) for patients (Mann Whitney U test; p=0.16). Finally, the median SE was 0.29 (IR 0.22–0.43) for the controls and 0.19 (IR 0.14–0.24) for the patients (Mann Whitney U test; p=0.03). See Figure 4.2 for boxplots of the above-mentioned analyses.

The CVs showed a significant mutual correlation. By contrast no significant correlation was found between the CVs and the corresponding SEs (see Table 4.1).

Table 4.1 Spearman's rank correlations between linear and nonlinear measurements

		Coefficient of variation	
	Sample entropy	CV IBI	CV amplitude (exp)
CV IBI	0.42 (p=0.10)		
CV amplitude (exp)	0.33 (p=0.21)	0.60 (p=0.02)*	
CV amplitude (insp)	0.31 (p=0.24)	0.72 (p<0.01)*	0.52 (p=0.04)*

CV, coefficient of variation; IBI, inter-breath interval.
* p<0.05.

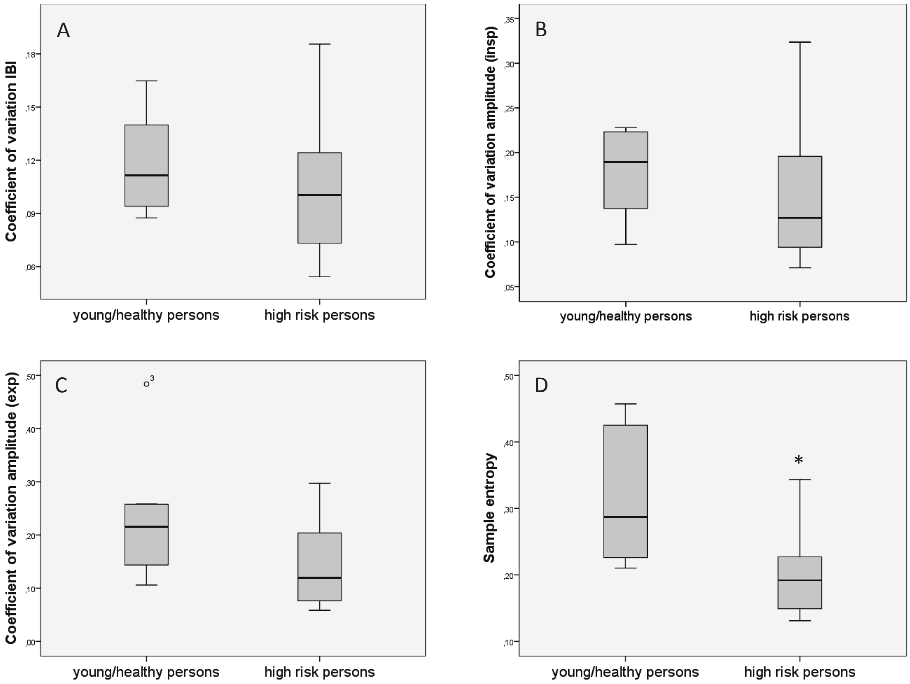

Figure 4.2 Boxplots showing the differences between persons at high risk for postoperative pulmonary complications and young/healthy controls for the coefficient of variation of the inter-beat interval (p=0.45) **(A)**, of the inspiratory amplitude (p=0.19) **(B)**, and of the expiratory amplitude (p=0.16) **(C)** as well as the sample entropy (p=0.03) **(D)**.

DISCUSSION

Our study demonstrates that variability and complexity-related measures of breathing patterns can be determined reliably even when using a brief recording protocol. A complexity-related measure, here the sample entropy, helped to distinguish between the control group, consisting of young and healthy volunteers, and the patient group with patients at high risk for postoperative pulmonary complications.

The brief recording protocol dictating eupneic breathing yielded stationary respiratory signals, which is prerequisite for all subsequent analysis, be it linear or nonlinear. By the same token, the sample was large enough to allow for reliable estimate of the complexity-related measure sample entropy.[1] In fact the entropies revealed more pronounced

[1] Other measures addressing the complexity of nonlinear dynamics like fractal dimensions or scaling characteristics of the autocorrelation (e.g. the Hurst exponent) typically require much longer (non-periodic) signals.

differences between controls and patients than coefficients of variations did. These findings agree with the idea that the respiration system is a biological system that is characterized by non-linear dynamics resulting in irregularity and complexity. The linear measures did show greater variability in the control group albeit less marked and in fact not significant (the latter maybe due to low power). The weak correlation between the linear and nonlinear measures may be considered indicative for their generic difference.[25] Investigating both sides of the coin, the linear and the nonlinear one, can thus provide additional insight in clinically relevant aspects of breathing patterns.

Variability and complexity of physiological signals in relation to pathology and aging has been investigated in detail for heart function by assessment of the heart rate variability (HRV)[26] but to a much lesser extent for respiratory function. While there are no studies investigating linear and nonlinear properties of respiratory signals for the purpose of risk stratification in abdominal and thoracic surgery, it is important to realize that our results agree with those found in other patient groups. Recently Veiga and co-workers demonstrated less nonlinear complexity in respiratory patterns in asthmatic patients with airway obstruction compared to healthy persons.[27] This study also computed the entropy by use of brief recordings. Furthermore, scaling exponents determined via detrended fluctuation analysis (DFA) of a two hours recording differed between healthy elderly male compared to young male in research of Peng.[12] Besides differences between patients and healthy controls, other studies focused on the assessment of the adaptive capacity of the respiratory system in order to distinguish patients who can be successfully separated from mechanical ventilation and who cannot. Recently, White and co-workers demonstrated lower sample entropy of the respiratory signal in patients who failed to separate from mechanical ventilation.[17] Interestingly, such weaning failure patients seem to exhibit significantly reduced sample entropy, Lyapunov exponents, and increased DFA exponents[18] suggesting non-trivial temporal correlations in the breathing patterns.

Such complex temporal characteristics in the mouth pressure signal may be attributed to both the output of the respiratory center in the brainstem and to lung mechanics (dynamic properties of the lung tissue and bronchial muscles). The latter's influence, however, appears limited since patients who are mechanically ventilated through a machine-controlled assistance mode without any variability, do not display any signs of complex dynamics. This advocates a neural origin of the here-discussed, complexity-related variability above mere mechanical features of the respiratory system.[28]

Our feasibility study compared variability and entropy of the respiratory signal of young and healthy persons with that of patients at risk for pulmonary complications based on consisting preoperative criteria. This is a first step in the development of a comprehensive assessment in the preoperative care that addresses the random and complex nature of breathing alike. For the sake of demonstration we chose to maximize contrast between the groups under study, i.e. young and healthy volunteers versus patients at high risk for postoperative pulmonary complications, most elderly and sometimes frail people. The promising results of our study call for investigating a less favorable contrast in the study population as present in elderly patients scheduled for major abdominal and thoracic surgery. Future research should also include the postoperative course as outcome measure for the validation of the use of linear and nonlinear measurements in the preoperative risk stratification. Finally, it is interesting to question if effects of inspiratory muscle training on postoperative pulmonary complications[5,29] can be associated with the non-linear dynamics of the respiratory signal. In fact, exercise has already been shown to improve the autonomous regulation of the heart as reflected by nonlinear indexes (DFA exponents and entropy measures) of the heart rate variability[30] but future study should address this in more detail.

Conclusion

We demonstrated the feasibility of linear and nonlinear measures in the preoperative assessment of the adaptive capacity of the respiratory system. Sample entropy of a brief sample of the respiratory pattern distinguished young and healthy persons from patients at high risk for postoperative pulmonary complications after major abdominal and thoracic surgery. Complexity-related measures of the respiratory system seem valid parameters for use in the risk stratification in the preoperative care of patients scheduled for major surgery affecting the postoperative respiratory function.

REFERENCES

1. Duggan M, Kavanagh BP. Pulmonary atelectasis: a pathogenic perioperative entity. Anesthesiology 2005;102:838-54.

2. Smith PR, Baig MA, Brito V, Bader F, Bergman MI, Alfonso A. Postoperative Pulmonary Complications after Laparotomy. Respiration 2010;80:269-74.

3. Rock P, Rich PB. Postoperative pulmonary complications. Curr Opin Anaesthesiol 2003;16:123-31.

4. Duggan M, Kavanagh BP. Perioperative modifications of respiratory function. Best Pract Res Clin Anaesthesiol 2010;24:145-55.
5. Dronkers J, Veldman A, Hoberg E, van der Waal C, van Meeteren N. Prevention of pulmonary complications after upper abdominal surgery by preoperative intensive inspiratory muscle training: a randomized controlled pilot study. Clin Rehabil 2008;22:134-42.
6. Dronkers JJ, Lamberts H, Reutelingsperger IM, et al. Preoperative therapeutic programme for elderly patients scheduled for elective abdominal oncological surgery: a randomized controlled pilot study. Clin Rehabil 2010;24:614-22.
7. Hulzebos EH, Helders PJ, Favie NJ, De Bie RA, Brutel de la Riviere A, Van Meeteren NL. Preoperative intensive inspiratory muscle training to prevent postoperative pulmonary complications in high-risk patients undergoing CABG surgery: a randomized clinical trial. JAMA 2006;296:1851-7.
8. Valkenet K, van de Port IG, Dronkers JJ, de Vries WR, Lindeman E, Backx FJ. Preoperative exercise therapy: better postoperative outcome? A systematic review. Clin Rehabil 2011;25:9-111.
9. Glass L. Synchronization and rhythmic processes in physiology. Nature 2001;410:277-84.
10. Haken H. A Top-Down Approach to Neural Nets; 2004.
11. Thurner S, Mittermaier C, Ehrenberger K. Change of complexity patterns in human posture during aging. Audiol Neurootol 2002;7:240-8.
12. Peng CK, Mietus JE, Liu Y, et al. Quantifying fractal dynamics of human respiration: age and gender effects. Ann Biomed Eng 2002;30:683-92.
13. Lipsitz LA. Dynamics of stability: the physiologic basis of functional health and frailty. JGerontolA BiolSciMedSci 2002;57:B115-B25.
14. Frey U, Maksym G, Suki B. Temporal complexity in clinical manifestations of lung disease. J Appl Physiol 2011;110:1723-31.
15. Caldirola D, Bellodi L, Caumo A, Migliarese G, Perna G. Approximate entropy of respiratory patterns in panic disorder. AJ Psychiatry 2004;161:79-87.
16. Vaillancourt DE, Newell KM. Changing complexity in human behavior and physiology through aging and disease. Neurobiol Aging 2002;23:1-11.
17. White CE, Batchinsky AI, Necsoiu C, et al. Lower interbreath interval complexity is associated with extubation failure in mechanically ventilated patients during spontaneous breathing trials. J Trauma 2010;68:1310-6.
18. Papaioannou VE, Chouvarda IG, Maglaveras NK, Pneumatikos IA. Study of multiparameter respiratory pattern complexity in surgical critically ill patients during weaning trials. BMC Physiol 2011;11:2.

19. Richman JS, Moorman JR. Physiological time-series analysis using approximate entropy and sample entropy. Am J Physiol Heart Circ Physiol 2000;278:H2039-49.

20. Leung AM, Gibbons RL, Vu HN. Predictors of length of stay following colorectal resection for neoplasms in 183 Veterans Affairs patients. World J Surg 2009;33:2183-8.

21. Smetana GW, Lawrence VA, Cornell JE. Preoperative pulmonary risk stratification for noncardiothoracic surgery: systematic review for the American College of Physicians. Ann Intern Med 2006;144:581-95.

22. Kennedy GD, Rajamanickam V, O'Connor E S, et al. Optimizing Surgical Care of Colon Cancer in the Older Adult Population. Ann Surg 2011;253:508-14.

23. Chen X, Chon KH, Solomon IC. Chemical activation of pre-Botzinger complex in vivo reduces respiratory network complexity. Am J Physiol Regul Integr Comp Physiol 2005;288:R1237-47.

24. Lake DE, Richman JS, Griffin MP, Moorman JR. Sample entropy analysis of neonatal heart rate variability. Am J Physiol Regul Integr Comp Physiol 2002;283:R789-97.

25. Korhonen I, Mainardi L, Ypparila H, Musialowicz T. Comparison of linear and non-linear analysis of heart rate variability in sedated cardiac surgery patients. In; 2001: IEEE; 2001. p. 496-9 vol. 1.

26. Voss A, Heitmann A, Schroeder R, Peters A, Perz S. Short-term heart rate variability-age dependence in healthy subjects. Physiol Meas 2012;33:1289-311.

27. Veiga J, Lopes AJ, Jansen JM, Melo PL. Airflow pattern complexity and airway obstruction in asthma. J Appl Physiol 2011;111:412-9.

28. Mangin L, Fiamma MN, Straus C, et al. Source of human ventilatory chaos: lessons from switching controlled mechanical ventilation to inspiratory pressure support in critically ill patients. Respir Physiol Neurobiol 2008;161:189-96.

29. Hulzebos EH, van Meeteren NL, van den Buijs BJ, De Bie RA, Brutel de la RA, Helders PJ. Feasibility of preoperative inspiratory muscle training in patients undergoing coronary artery bypass surgery with a high risk of postoperative pulmonary complications: a randomized controlled pilot study. Clin Rehabil 2006;20:949-59.

30. Mendes RG, Simoes RP, De Souza Melo Costa F, et al. Short-term supervised inpatient physiotherapy exercise protocol improves cardiac autonomic function after coronary artery bypass graft surgery--a randomised controlled trial. Disabil Rehabil 2010;32:1320-7.