Non-linear dynamics of cardiovascular system in humans exposed to repetitive apneas modeling obstructive sleep apnea: aggregated time series data analysis

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Abstract

Objective: Testing the hypothesis that alterations in non-linear dynamics of the cardiovascular variability appear in healthy, awake subjects during voluntary apnea. Subjects and Methods: Ten young subjects performed 20 apneas 60 s each separated by 1 min free breathing. Inter-beat interval (IBI) measured as RR-interval in ECG, systolic (SYS) and diastolic (DIAS) arterial blood pressure, stroke volume (SV), cardiac output (CO) and total peripheral resistance (TPR) were non-invasively recorded and computed by Portapress 2 system. Correlation dimension according to Grassberger–Procaccia algorithm (CD) and ratio of % determinism versus % recurrence (RDR) computed from recurrence plot according to Webber and Zbiluth J. Appl. Physiol. 76 (1994) 965 were used as the indices of chaos and complexity. Sequential time series of cardiovascular variables in consecutive 60-s apneas and inter-apnea free breathings were separately windowed and aggregated. CD and RDR of aggregated apneic time series were compared with CD and RDR values of aggregated time series of inter-apnea free breathing, 10 min at rest and 10 min recovery. Reliability of the aggregation method of sequential time series was tested on transformed simulated data generated by Lorenz model. Error in CD and RDR estimation did not exceed 5% and 1%, respectively. Results: CD of cardiovascular variables computed from aggregated apneas was significantly reduced and RDR augmented versus control and recovery periods. CD and RDR values of inter-apnea phases were in between those in control and during apneas. Time domain linear variance (SD) was increased during aggregated apneas. Conclusions: Signal dynamics dependent windowing and data aggregation could be a useful tool for non-linear analysis of short repeatable sequential time series; time domain linear variability of the cardiovascular dynamics is augmented while complexity reduced during apneic chemoreceptor stimulation; alterations in non-linear dynamics of cardiovascular variables during apneas in healthy normotensive subjects may suggest an early sign of a mechanism implicated in arterial hypertension in OSAS.

Keywords: Circulatory response to apnea; Non-linear dynamics; Aggregated time series data; Correlation dimension; Recurrence plot; Humans

1. Introduction

Obstructive sleep apnea (OSA) is associated with arterial hypertension (Kales et al., 1984; Hla et al., 1994). Augmented sympathetic activity (Carlson et al., 1993; Somers et al., 1995), due mainly to tonic sympathoexcitatory arterial chemoreceptor drive (Narkiewicz et al., 1998a) and selective potentiation of hypoxia-induced pressor and sympathoexcitatory chemoreflex (Hedner et al., 1992; Narkiewicz et al., 1999), was reported in OSA patients also in day time, a finding similar to potentiation of chemoreceptor reflex in mild and borderline primary hypertension (Somers et al., 1988; Trzebski et al., 1982). Mechanisms of OSA-dependent arterial hypertension are unknown. A long-term facilitation of arterial chemoreceptor reflex has been suggested (Narkiewicz et al., 1999; Trzebski, 1992; Trzebski and Śmiatanowski, 1996a). Augmented variability of nocturnal heart rate characterizes OSA patients (Roche et al., 1999). Narkiewicz et al. (1998b) found in awake OSA patients, even in the absence of arterial hypertension, an increased variability in frequency domain of power spectra of arterial blood pressure and resting sympathetic activity with accompanying increase in the ratio of low to high frequency power LF/HF, an index of sympathetic overactivity (Pagani et al., 1997). Voluntary apnea augments absolute value of LF power in spectra of heart rate, systolic and diastolic blood pressure in healthy subjects, a finding suggesting that LF oscilla-
tions during apnea exhibit a central endogenic autonomic rhythm controlling cardiovascular system (Cooley et al., 1998; Trzebski and Śmiatanowski, 1996b). Shiomi et al. (1996) observed a significant increase in very low frequency component of heart rate power spectra synchronized with apneic episodes during nocturnal sleep in OSAS patients. This observation may suggest non-linear, chaotic behavior of the cardiovascular control system during apnea.

Biological systems are complex and non-linear as a rule. Techniques adopted from chaos theory provide some information on the complexity of the system by extracting information from time series of a single variable. Their usefulness has been confirmed in cardiology, as reduced complexity of heart rate is a risk stratification factor (Wagner and Persson, 1998).

The purpose of this paper was to apply tools of non-linear dynamics to assess complexity of the cardiovascular control system during each windowed apnea.

2. Subjects and methods

The study was carried out on 10 young normotensive medical students (mean systolic blood pressure $121 \pm 6.9$...
mmHg, diastolic pressure 80.1 ± 3.3 mmHg), seven males and three girls aged 19–24 years (mean 21.1 ± 2.23), of normal BMI, free of any diseases or medical treatment, either history of alcohol or drug abuse, without regular sport activities. Written informed consent was obtained from all subjects. Measurements were performed before noon or in early afternoon. After 15–20 min adaptation to laboratory conditions, the subjects adopted sitting position with the forearm posed on the heart level. The finger blood pressure was recorded by Portapress 2 system compensating for position changes and recalibration artifacts. Stroke volume was continuously computed from the blood pressure curve according to Wesseling model (Wesseling et al., 1993) programmed in the system. Instantaneous cardiac output and total peripheral vascular resistance for each heartbeat were computed off line. Oxygen saturation was recorded by DATEX pulsoxymeter placed on the finger. Respiratory activity was monitored by nasal airflow measured by temperature-sensitive thermocouples. After 10-min recording during control breathing at rest (C), each subject hold breathing in quiet inspiration for 60 s (A). Breathing was resumed and after 1 min (B) stopped again. In each experiment, 20 repetitive apneas and 19 inter-apnea free breathing periods have been imposed. After the last apnea, cardiovascular variables were still recorded for another 10 min of recovery period (R). Each experiment lasted for 1 h.

Analogue signals (ECG, blood pressure, respiratory activity and blood oxygen saturation) were digitized (Spike-2, CED, England) with, respectively, 500, 125, 10, 10 Hz sampling frequency and saved for further off-line analysis (FAST-Holland, MATLAB-USA). Spike-2 was used for R-waves identification in ECG, apnea, inter-apnea period onset in respiratory activity signal and further visual inspection of artifacts. Beat-to-beat data calculated by FAST program (SYS, DIAS, HR, IBI, SV, CO, TPR), continua-

![Cardiovascular variables during single apnea](image_url)

Fig. 2. Cardiovascular variables during single apnea. From bottom: continuously recorded respiratory activity (resp), blood oxygen saturation (spo2) and finger arterial blood pressure (bp) synchronized with calculated beat-to-beat total peripheral resistance (tpr), cardiac output (co), diastolic blood pressure (dias), systolic blood pressure (sys) and inter-beat intervals (ibi). Discontinuities in blood pressure signal are due to self-calibration (Physiocal) of Portapress 2 system and are automatically compensated in beat-to-beat analysis output.
ously recorded signals by Spike-2, RR, apnea and inter-apnea period markers time intervals were synchronized and saved in MATLAB format.

2.1. Analysis and statistics

Most of non-linear parameter estimation procedures deserve theoretically infinite and practically large samples of data. Short time series are not suitable for this kind of analysis. However, we assumed that cardiovascular changes induced in observed signal dynamics by 60 s long apneas may represent fragments of the same yet interrupted process. On this assumption, the method of dynamics dependent windowing and data aggregation procedure was applied (Smietanowski, 2001). This new approach was tested on chaotic signal generated by Lorenz model. ‘Mixed-up’ and ‘stroboscope windowed’ testing signals were applied to investigate CD and RDR dependence on disrupted time sequence and segmentation–aggregation procedure. Original Lorenz time series data (4000 points) was divided into 20 equal segments of which 10 from the beginning were randomly ordered to form Mixed-up, 2000 points long testing signal. Transformed Lorenz model output by division it into 40 equal segments of which every second, in order of appearing in original data, was used to create aggregated 2000 points long stroboscope windowed testing signal. Preliminary results of the simulated time series analysis seem to support our assumption about possible assessment of non-linear parameters in short repeatable time series by aggregation technique. Excursion from theoretical and calculated CD for testing signals was less than 5% for 2000 points sample length and relative difference

Fig. 3. Running 1-min window averages time course in control (C), during sequential apneas (A) and in the recovery period (R) for cardiovascular parameters in all subjects. Whiskers mark standard errors calculated parallel with averages. Longer distance between circles in A are due to exclusion of inter-apnea periods from calculations.
between RDR for original and transformed model data was about 1% independently on sample length (600, 1200, 2000 points).

By using respiratory signal as a reference, all cardiovascular variables were segmented and aggregated into four sections: control (C), aggregated apnea phase (A), inter-apnea period (gray bar) and r—in the recovery period (hatched bar). From the top: iibi—inter-beat interval, sv—stroke volume, sys—systolic blood pressure, co—cardiac output, dias—diastolic blood pressure, tpr—total peripheral resistance. Statistical significance of differences marked by asterisks.

* P<0.05

Fig. 4. Mean values of correlation dimension of cardiovascular variables in c—control (white bar), a—during aggregated apneas (black bar), b—during inter-apnea period (gray bar) and r—in the recovery period (hatched bar). From the top: iibi—inter-beat interval, sv—stroke volume, sys—systolic blood pressure, co—cardiac output, dias—diastolic blood pressure, tpr—total peripheral resistance. Statistical significance of differences marked by asterisks.
aggregated inter-apnea phase (B) and recovery (R). To avoid transients, the first five beats at the onset of apnea were rejected. The scheme of data segmentation and aggregation by example of IBI signal is presented in Fig. 1. After preprocessing, correlation dimension calculation and recurrence plot strategy was applied to each of the four phases separately. Surrogate data analysis was performed each time to confirm validity of results.

Means, standard deviations (SD), standard errors (SE) were estimated for whole set of each calculated parameter.

![Graphs showing the ratio of % determinism vs. % recurrence of recurrence plots of cardiovascular variables.](image)

Fig. 5. Mean values of ratio (% determinism vs. % recurrence of recurrence plots of cardiovascular variables). Symbol descriptions as in Fig. 4.
Running average (1-min window) and running standard deviation over time of registration for all subjects were determined by means of standard MATLAB procedures (Matlab Statistics Toolbox, User’s Guide, MathWorks, 1997).

Difference in means was investigated by \( t \)-test for correlated samples at significance level of 0.05 considering possible inhomogeneity of variance (Ferguson and Takane, 1989).

3. Results

3.1. Hemodynamic response to voluntary apnea

In all subjects, systolic (SYS) and diastolic (DIAS) blood pressure were increasing during apnea reaching the peak value up to 5 s after termination of apnea at the onset of rebreathing. Heart rate in apnea was less regular. It usually slowed down in the second half of apneic period,

Fig. 6. Mean standard deviations of cardiovascular variables. Symbol descriptions as in Fig. 4.

* P<0.05
yet in some subjects who experienced strong dyspnea, heart rate increased in the last 20–30 s of apnea (Fig. 2). A peak high heart rate appeared immediately after resumption of breathing. Further cardiac acceleration was noted during the pressure drop following early blood pressure peak after apnea (Fig. 2). Stroke volume (SV) was reduced significantly in apnea. Total peripheral resistance (TPR) increased progressively during apnea yet in some cases reached the peak before the end of apneic period and decreased parallel with some increase of cardiac output (CO) prior to the end of apnea. Increasing heart rate in some subjects at the end of apnea accounts probably for slight augmentation in cardiac output and consequently, slight decrease in computed TPR at the end of breath holding (Fig. 2). However, absolute TPR values were always significantly higher and those of CO lower during apnea and reached nadir in 5–10 s after the apnea Fig. 2. However, absolute TPR values were always significantly higher and those of CO lower during apnea than at rest prior to apnea. Decrease of oxygen hemoglobin desaturation was evident in the second half of apnea and reached nadir in 5–10 s after the apnea (Fig. 2). This delay, due probably to lung–fingertip circulation time and inertia of the recording system, is not in disagreement with similar delays observed in subjects breathing hypoxic gas mixture prior to voluntary apnea (Watenpaugh et al., 1999). Fig. 3 presents summarized mean data recorded in all experiments during 1 h.

3.2. Correlation dimension and recurrence plot analysis

Correlation dimension (CD) computed from mean 1493 data points ± 83 SD in aggregated apneic time series was significantly reduced for all cardiovascular variables. Mean value of CD for systolic arterial blood pressure (SYS) dropped from 7.23 ± 0.50 in the control (C) to 4.52 ± 0.40 during aggregated apneas (A), 6.05 ± 0.52 during aggregated inter-apnea periods (B) and 7.53 ± 0.51 in the recovery period (R). Correspondingly, mean CD of diastolic blood pressure (DIAS) time series dropped from 7.91 ± 0.54 (C) to 4.82 ± 0.39 (A), 6.58 ± 0.52 (B) and 7.50 ± 0.82 (R). Respective values of CD for inter-beat intervals (IBI) were: 10.49 ± 0.81 (C), 6.84 ± 0.64 (A), 10.82 ± 1.05 (B) and 9.46 ± 0.89 (C). Mean CD values of stroke volume (SV) time series were: 13.17 ± 0.48 (C), 6.52 ± 0.46 (A), 11.40 ± 1.04 (B) and 13.00 ± 1.06 (R). Mean CD for cardiac output time series (CO) dropped from 10.24 ± 0.78 (C) to 6.34 ± 0.41 (A), 8.79 ± 0.68 (B) and 9.42 ± 0.70 (R). Respective values of mean CD for total peripheral resistance (TPR) time series were: 8.71 ± 1.05 (C), 5.56 ± 0.48 (A), 7.12 ± 0.47 (B), 7.90 ± 0.56 (R).

Graphical presentation of above data and statistical significance of differences of means are shown in Fig. 4. Correlation dimensions computed from time series of all cardiovascular variables were reduced during apnea versus control and recovery. Correlation dimensions of aggregated inter-apnea time series were significantly reduced only for cardiac output and total peripheral resistance. All variables had a significantly lower correlation dimension during aggregated apneic periods than CD for inter-apnea aggregated free breathing phases. Except for inter-beat interval (IBI), CD of all cardiovascular variables were lower during inter-apnea periods than during recovery period. However, the difference was significant only for systolic blood pressure and stroke volume.

Respective mean values for the ratio of % determinism versus % recurrence (RDR) were for systolic arterial blood pressure (SYS): 4.44 ± 0.21 (C), 5.32 ± 0.58 (A), 5.14 ± 0.35 (B) and 4.08 ± 0.30 (R); for diastolic blood pressure (DIAS): 3.94 ± 0.24 (C), 4.64 ± 0.28 (A), 4.66 ± 0.18 (B) and 3.76 ± 0.24 (R); for inter-beat interval (IBI): 3.20 ± 0.26 (C), 4.95 ± 0.24 (A), 3.70 ± 0.38 (B) and 3.82 ± 0.32 (R); for stroke volume (SV): 3.23 ± 0.30 (C), 5.74 ± 4.11 (A), 4.11 ± 0.41 (B) and 3.72 ± 0.50 (R); for total peripheral resistance (TPR) time series: 4.30 ± 0.26 (C), 5.13 ± 0.13 (A), 5.24 ± 0.32 (B) and 5.15 ± 0.40 (R).

Fig. 5 presents diagrams and significance of RDR differences. Ratio of % determinism versus % recurrence (RDR) of recurrence plots was significantly augmented for time series of all cardiovascular variables during aggregated apneic periods compared to control period except of that for systolic blood pressure. Augmentation of RDR of total peripheral resistance outlasted significantly apneic and inter-apnea periods and was still evident during 10 min of recovery.

Standard deviation (SD), a linear time domain measure of variability of all cardiovascular variables, was slightly yet significantly augmented during aggregated apneas compared to control resting period except of SD of inter-beat intervals (IBI). However, SD of IBI values was also augmented significantly in the aggregated inter-apnea periods (Fig. 6).

4. Discussion

Present results provide the first analysis of non-linear dynamics and chaotic behavior of the cardiovascular control system during apnea in humans. In our previous study, we shown that correlation dimension (CD) of the arterial blood pressure and total vascular resistance (TPR) computed from time series within 20-min continuous periods of alternating voluntary apneas and free breathings was significantly reduced in young subjects (Trzebski et al., 1998; Trzebski et al., 1992). However, non-linear dynamics of the cardiovascular variables during isolated apnea has been unknown. Our present data suggest that within apnea itself, the complexity of the cardiovascular control system is reduced. It may appear surprising that under chemoreceptor stimulation, recruiting many circulatory central and peripheral feedbacks the system as a whole appears less complex. One of the reasons may be the attenuation or inhibition of the arterial baroreflex by chemoreceptor stimulation. Hypoxic stimulation of arterial chemoreceptors significantly reduces the gain of cardiova-
gal and inhibitory blood pressure baroreflex activated by neck suction method (Tafil and Trzebski, 1984). There is a specific antagonistic interaction between baroreceptor reflex and chemoreceptor sympathoexcitatory reflex in humans (Somers et al., 1991). After termination of apnea, a peak pressor response coincides with inhibition of sympathetic nerve activity. Apparently, arterial baroreflex and/or lung inflation reflexes dominate over chemoreceptor sympathoexcitatory reflex in awake healthy patients after apnea (Wartenpau et al., 1999). However, this relation may be reversed after facilitation of chemoreflex by intermittent repetitive stimulations of chemoreceptors which induce potentiation of the sympathoexcitatory chemoreflex in OSA patients (Narkiewicz et al., 1999). Indeed, Carlson et al. (1996) have shown that OSA patients exhibit an impaired baroreflex sensitivity which may contribute to augmented resting sympathetic activity.

Baroreceptor reflex plays crucial role as a significant negative feedback of cardiovascular control system and appears to contribute to non-linear behavior of heart rate in humans (Wagner and Persson, 1998) and chaotic behavior of arterial blood pressure (Wagner et al., 1995). Attenuation of baroreceptor reflex by increased peripheral chemoreceptor reflex drive could account for reduced complexity of the cardiovascular control system during apnea.

To focus on chemoreceptor stimulation during apnea, we tried to avoid any mechanical factors and to remain only sympathoexcitatory chemoreflex induced by combined multiplicative hypoxic and hypercapnic stimulation (Morgan et al., 1995; Trzebski et al., 1995). Voluntary apnea applied in the present study differs from obstructive sleep apnea (OSA) as our subjects avoided inspiratory movements (Mueller maneuver). Carotid chemoreceptor stimulation is a primary mechanism responsible for apnea-induced sympathoexcitatory activation during wakefulness as mechanical factors play a minor role (Kattragadda et al., 1997; Morgan et al., 1993).

We were taking into account implications of augmented arterial chemoreceptor sympathoexcitatory drive in the pathogenesis of arterial hypertension (Trzebski, 1992). In essential human hypertension correlation dimension (CD) of arterial blood pressure is reduced (Kagiyama et al., 1999) along with the impairment (resetting) of baroreflex (for review, see Eckberg and Sleigt, 1992) and augmented resting sympathetic activity (Mark, 1996). Such similarities provoke an attractive hypothesis that obstructive sleep apnea syndrome (OSAS) triggers a mechanism close to that which contributes to primary hypertension. For the same reason, patients with a genetic risk of primary hypertension would be prone to OSA-induced hypertension. This hypothesis requires further research.

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