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PATTERN RECOGNITION APPROACH FOR ANALYSIS OF METABOLIC RESPONSE TO INTERMITTENT HYPOXIA

Intermittent hypoxia (IH) elicits two forms of respiratory plasticity, which are initiated during and after exposure to IH, i.e. a long-term facilitation and a progressive augmentation of respiratory motor output. IH is often used as a model of sleep apnea and/or respiratory plasticity in humans and animals. Procedures of IH are also applied in sport medicine and rehabilitation of respiratory diseases. The aim of the present paper is an analysis of a metabolic response to acute intermittent hypoxia in a rat model. The animals were placed and monitored in a whole body plethysmographic chamber. The rats were exposed to five consecutive cycles consisting of 10-min hypoxic stimulus period separated by 10-min normoxic intervals, and additionally they were monitored up to 1 h after the final hypoxic exposure. The metabolism software analyzer recorded following variables (features): metabolic rate, carbon dioxide production, oxygen consumption and respiratory quotient. The obtained results demonstrated that acute IH causes metabolic effects during and after intermittent stimuli, which may be effectively recognized by an application of the *k*-NN classifiers.

1. INTRODUCTION

Hypoxia, i.e. decreased O_2 availability, is a stimulus that affects biological systems, and may act as acute or chronic exposition [4, 11, 33]. Systemic responses to acute hypoxia occur within seconds and are mediated entirely by reflexes originating from peripheral chemoreceptors the carotid body [11]. On the other hand, chronic persisting for several hours to days leads to phenotype re-modeling and adaptation of physiological systems, which require activation of transcription factors most notably the hypoxic inducible factor-1 (HIF-1) [26]. HIFs are heterodimeric proteins composed of subunits: α (HIF-α) and β (HIF-β) [35]. HIF-1α and HIF-2α are major isoforms of α subunit. Analysis of human cancer biopsies *versus* surrounding normal tissue shows, for example, that the expression of HIF-1α or HIF-2α is significantly increased in the majority of cancers and their metastases [32, 36]. Drugs targeted for HIF-1 inhibition are tested as anticancer agents in clinical trials [16, 25]. Furthermore, recent studies have demonstrated also different effects of intermittent hypoxic stimulus, in the course of hypoxia-reoxygenation cycles [17, 19, 23].

Intermittent hypoxia (IH) may induce two forms of respiratory plasticity, which are initiated after and/or during exposure to IH, such as a long-term facilitation (LTF) and a progressive augmentation of respiratory motor output [12, 15, 30]. Long-term facilitation is characterized by a sustained elevation of respiratory activity after exposure to intermittent hypoxia. Progressive augmentation is characterized by a gradual increase in respiratory activity from the first to the final hypoxic exposure. IH is often applied as a model of sleep apnea disorders and/or respiratory neuroplasticity [17, 19, 23]. Mahamed and Mitchell [13] suggest that repeated sleep apneas cause IH, and enhanced LTF may compensate for factors that predispose to sleep-disordered breathing. Other researches show that intermittent hypoxia can positively modulate tumour development, inducing tumor growth, angiogenic process, chemoresistance, and radioresistance [1, 14, 34]. Their results suggest that HIF-1α stabilization occurring as a consequence of IH may be an important cause for new anticancer therapies. Reactive oxygen species (ROS) generated during the reoxygenation periods can also play an important role, modifying gene expression through the regulation of the activity of some transcription factors, such as activator protein-1 (AP-1) or nuclear factor kappaB (NF-κB). Furthermore, intermittent hypoxic training (IHT) is a novel physiologic and therapeutic approach in sport medicine and several respiratory disorders [18, 27, 28]. Additionally, the

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studies are potentially worth area to test usefully several computer algorithms and systems for monitoring and evaluating some effects of intermittent hypoxia and/or apnea in physiology and respiratory pathologies [5, 6, 29]. However, effects of IH, which are more prevalent condition in health and disease, are still currently unknown.

In our previous experimental studies, we analyzed ventilatory response to acute intermittent hypoxia in anesthetized rabbits [29, 30] and awake rats [31]. In this study, to evaluate the metabolic effects of acute IH, we decided to use pattern recognition methods based on the *k* nearest neighbor (*k*-NN) rule. This rule is simultaneously very simple and very powerful and can be treated as an approximation of the best, theoretically possible, Bayes classifier [2]. However, there exist several possibilities of exploring this rule in the classifier construction. For instance, it can be used as a standard classifier [3], fuzzy *k*-NN rule [7, 10], multistage classifier [8] or as a parallel net of two-decision k-NN component classifiers, i.e. pair-wise *k*-NN classifier [9].

The standard and the pair-wise version of the *k*-NN classifier are used in the present paper. In the case of the pair-wise structure a separate *k*-NN classifier is constructed for each class pair. The final decision is formed by voting of the component two-decision classifiers. In previous author's work [9] each of the component classifier was giving its whole voice in favor to one of two classes. However, the *k*-NN rule produces in fact fuzzy decision. As a membership v_j to the class j a ratio k_j/k is assumed, where k_j is the number of object from the class j from among of k nearest neighbors. All values k_j/k form components of the fuzzy membership decision-vector. So, the classifier decision expressed as a class membership vector is distributed among all classes and $\sum_{j=1,nc}^{nc} v_j=1$. If one is interested in receiving a crisp (non-fuzzy) decision then the classifier assigns the class that corresponds to the highest value of v_j. In case of the mentioned component classifiers their votes are shared among two classes. The fuzzy membership vector corresponding to the pair of classes i and j has the following form: $\mathbf{v}_{ij}=[0_1,\dots,0_{i-1},v_i,0_{i+1}\dots,0_{j-1},v_j,0_{j+1}\dots,0_{nc}]$, where nc is number of classes, $v_i+v_j=1$ and all components of this vector, except those on positions i and j are zeros. Using membership vectors for the component classifier, the final fuzzy decision can be obtained as a mean of $nc*(nc-1)/2$ membership vectors $\mathbf{v}_{ij}$, $i,j=1,2,..,nc$, $i<j$, and next from this vector the crisp decision can be received.

The analysis of metabolic response to the intermittent hypoxia in an animal model is the aim of the study. We studied metabolic changes by a whole body plethysmography during and after acute intermittent hypoxia. We verified hypothesis that the observed metabolic changes in different periods of IH model of respiratory plasticity can be effectively distinguished by the pattern recognition approach.

2. BIOLOGICAL EXPERIMENTS AND METABOLIC MEASUREMENTS

The study was approved by a local Ethics Committee. Five independent experiments were performed in awake adult male Wistar rats (weight range 296-316g). The animals were placed and continuously monitored in a whole body plethysmographic chamber (model PLY3223, Buxco Electronics, Wilmigton NC with data analysis software of Biosytsem XA for Windows SF2T3410 v. 2.9). Whole body plethysmography (WBP) has been proven as a very useful tool in the study of breathing and metabolism. The main advantage of the WBP technique is that it is non-invasive and therefore enables long-term recordings from unanaesthetised and unrestrained subjects. The animals were exposed to acute moderate intermittent hypoxia (14% O_2, balance N_2). The protocol of IH consisted of 5 cycles of 10-min hypoxic exposures with 10-min air normoxic intervals. At least 1 h before the start of each protocol, the animals were allowed to acclimate to the chamber.

For plethysmograph signals, data from the last four minutes of all experimental periods were binded into 30-s samples and averaged (8 values were measured in each of the period). The metabolism software analyzer recorded the following parameters: metabolic rate, MR (feature 1); carbon dioxide production, VCO_2 (feature 2); oxygen consumption, VO_2 (feature 3); and respiratory quotient, RQ (was determined by dividing VCO_2 by VO_2, feature 4). VCO_2 and VO_2 values were corrected for body weight. Baseline level (i.e. base control) was evaluated before exposures to the IH in each rat. The following periods were concerned as the classes: the base control - class I; first and final (fifth) exposures of hypoxic stimulus -

class II and III, respectively; normoxic phase after last hypoxic exposure - class IV; and 1 h recovery normoxic period after the last hypoxic stimulus - class V. The considered features and classes are gathered in Table 1.

Table 1. Description of analyzed features and classes.

Features (physiological variables)	Classes (IH periods)
1. MR Metabolic rate 2. VCO_2 CO_2 production 3. VO_2 O_2 consumption 4. RQ Respiratory quotient	I. Baseline level II. First 10-min hypoxic episode III. Final 10-min hypoxic episode IV. 10-min normoxic period after last hypoxia V. 1-h recovery normoxic duration

3. RESULTS

The data analysis was started with evaluation of single features (i.e. MR, VCO_2, VO_2 and RQ as features 1, 2, 3 and 4 respectively) by the standard and the pair-wise classifier. Its result is presented in Table 2. The misclassification rates exceed 40% and are less than 53%, for each of the four features. It does not denote that there is no relation between the classes and the features. Without knowledge contained in the training set one could guest the right class (out of five) with the probability of 20%, what corresponds to the error rate of 80%, since the classes are of equal size in the training set. It is worth to notice that the pair-wise classifier is more flexible and a risk of overtraining is usually higher than in the case of the standard classifier. However, the size of the training set is sufficiently large in comparison with the number of features (50 times greater), so the chances of overtraining are rather low. It can be noticed that significance of all features is comparable and the error rates are remarkably lower for the pair-wise classifier. In spite of this, even the error rates offered by parallel classifier (i.e. pair-wise one) are too big to use any single feature for class distinguishing.

Table 2. Results obtained for single features with the use of the standard and the pair-wise classifier.

Feature	**Standard *k*-NN classifier**		**Pair-wise *k*-NN classifier**	
	Error rate	**Value of *k***	**Error rate**	**Value of *k*'s for class pairs**
1	0.530	4	0.485	*k*=6, 1, 13, 8, 1, 5, 8, 4, 4, 7
2	0.500	5	0.475	*k*=1, 54, 4, 1, 5, 10, 1, 7, 2, 9
3	0.420	1	0.405	*k*=1, 1, 4, 1, 1, 5, 3, 6, 1, 5
4	0.455	6	0.405	*k*=4, 14, 5, 7, 63, 1, 1, 2, 4, 6

Table 3. Results received by the use of the *k*-NN rule for the component classifiers of pair-wise classifier.

	Separate feature selection for each class pair			**All four features for each class pair**		
Column 1	Col. 2	Col. 3	Col. 4	Col. 5	Col. 6	Col. 7
Class pair	**Error rate**	**Value of *k***	**Selected features**	**Error rate**	***K***	**Features**
I, II	0.013	1	{1,4} or {2,4} or {3,4}	0.013	1	{1,2,3,4}
I, III	**0.025**	1	{1,2} or {2,4}	**0.038**	1	{1,2,3,4}
I, IV	0.000	1	{2,4}	0.000	1	{1,2,3,4}
I, V	0.013	1	{1,4} or {2,4} or {3,4}	0.013	1	{1,2,3,4}
II, III	0.075	1	{1,2,3,4}	0.075	1	{1,2,3,4}
II, IV	0.000	1	{1,4} or {2,4} or {3,4} or {2,3}	0.000	1	{1,2,3,4}
II, V	0.000	1	{1,3} or {1,4} or {2,4} or {3,4}	0.000	8	{1,2,3,4}
III, IV	**0.013**	1	{2,4}	**0.025**	1	{1,2,3,4}
III, V	0.000	2	{1,2} or {1,4}, {2,4} or {2,3} or {3,4}	0.000	2	{1,2,3,4}
IV, V	0.013	2	{1,4} or {2,4} or {3,4}	0.013	1	{1,2,3,4}

In case of the use of pair-wise classifier and all four features, it is worth to perform a separate feature selection for each of the component classifiers, not only to reduce the costs of measurements but also to improve the classification quality. The columns 2, 3 and 4 of Table 3 contain the results of feature selection and determination, for each selected feature combination, the optimum value of *k*. As implies from the column 4, the measurements of all 4 features are necessary in spite of feature selection. Without feature selection the error rates for two pairs (I, III) and (III, IV) marked in bold, are remarkably higher.

It was rather a big surprise that most *k*'s were equal 1 or 2 and only in one case *k*=8. In such situations no significant difference between the results for the pair-wise classifier with crisp and fuzzy voting can be expected.

It is easy to notice that if all *k*'s would be equal to 1 then no difference would appear between the crisp and fuzzy voting. In case of the analyzed data, as it is shown in the Table 4, the difference between the standard and the pair-wise classifier is not great. The standard *k*-NN rule allows to omit the measurement of feature 1 (MR) if the classification will be based on the features 2 (VCO_2) and 4 (RQ). Feature selection slightly decreased the error rate in case of the standard classifier. The misclassification rates for the pair-wise classification were the same whether feature selection was performed or not, although, as it was mentioned above, the error rates for class pairs were higher if the feature selection was omitted.

Table 4. Comparison of the standard and the parallel classifier for complete and selected feature sets.

Classifier type		Error rate	Features
No. 1	Standard *k*-NN, no feature selection	0.060	1, 2, 3, 4 (all)
No. 2	Standard *k*-NN, feature selection performed	0.055	2, 4 (selected)
No. 3	Pair-wise *k*-NN, no feature selection	0.050	1, 2, 3, 4 (all)
No. 4	Pair-wise *k*-NN, feature selection performed	0.050	1, 2, 3, 4 (selected)

The confusion matrices, shown in Table 5, were the same as for selected features as well as for classification based on all features. The most difficult for recognition was class II, 90% of cases were correctly classified and 10% were misclassified to the class III (Table 5a).

Table 5. Comparison of the standard and the parallel classifier for complete and selected feature sets.

(a) Probabilities that an object assigned to the class *i* is in fact from the class *j* [%]

Assigned Class	True class I	II	III	IV	V
I	95.1	0.0	2.5	0.0	2.5
II	0.0	90.0	10.0	0.0	0.0
III	0.0	5.0	95.0	0.0	0.0
IV	0.0	0.0	2.5	97.5	0.0
V	0.0	0.0	0.0	2.5	97.5

(b) Probabilities that an object assigned to the class *i* is in fact from the class *j* [%]

Assigned Class	True class I	II	III	IV	V
I	100	0.0	0.0	0.0	0.0
II	0.0	94.7	5.3	0.0	0.0
III	2.3	9.0	86.4	2.3	0.0
IV	0.0	0.0	0.0	97.5	2.5
V	2.5	0.0	0.0	0.0	97.5

It also means that from among samples assigned to the class III the percentage of correctly classified samples is the lowest and the most of misclassified samples, i.e. 9%, comes from the class II.

4. DISCUSSION

People experience chronic intermittent hypoxia (CIH) as a result of sleep-disordered breathing appeared as recurrent apneas (RA) [13, 15, 19, 20]. The chronic IH leads to serious cardio-respiratory changes, such as hypertension, persistent activation of sympathetic nervous system, and abnormalities in respiration. The CIH consequences are in part due to induction of functional plasticity in chemo-reflex pathway manifested as long-term facilitation (LTF) of carotid body sensor activity, and respiratory/sympathetic motor output. Prabhakar and colleagues [21, 22] suggest that reactive oxygen species (ROS) and the metabolites of molecular O_2, play a novel role as amplifiers of brief hypoxic signals and mediate systemic and cellular responses to CIH resulting in morbidity associated with RA. Unlike chronic IH, acute IH occurs in several physiological situations. For instance, men experience acute intermittent hypoxia during swimming, and then apneas are triggered by naso-pharyngeal reflex and exhibit bradycardia during apneic episodes. The effects of acute IH are associated with progressive increase in ROS, and ROS scavengers prevent neuronal responses to acute IH [12, 22].

In our studies, we analyzed respiratory response to acute intermittent hypoxia in experimental conditions using pattern recognition methods. The similar bioinformatics approach with using computer-modeling techniques and machine-learning algorithms was presented, for example, in papers [24, 37].

The standard and the pair-wise classifier were used by the authors in a numerous applications. Nearly always the parallel net of two-decision *k*-NN classifiers outperformed the standard version of the *k*-NN classifier. The present results confirm this advantage of the classifier pair-wise version. Feature selection usually decreases the error rate, no matter whether the standard or the pair-wise version was applied. However, in the present study it was a case only for the standard classifier. In our case, feature selection consists in reviewing error rates, corresponding optimum values of *k*, for all feature combinations. An optimum value of *k*, for each reviewed feature combination, was established experimentally by the use of the leave one out method [3]. For the pair-wise classifier feature selection did not improve the classification quality and it was the same as for the complete feature set. Feature selection usually decreases also the number of features to be measured although this phenomenon did not appear in the presented results. The advantage of the standard *k*-NN rule consists in the lower number of selected features and this was the case in our analysis.

From the biological standpoint the performed analysis showed that each single of measured features recognized the IH periods with above 40% error rate. However, all features together as well as set of selected features allowed recognizing the periods very well, i.e. E_r=0.050. The air normoxic phases (baseline level, 10-min normoxic duration after final hypoxic exposure and normoxic recovery after 1h of IH exposure) were recognized better and E_r ranged from 0.000 to 0.013. The differentiation between the first and the final hypoxic stimulus could be done with the error rate of 0.075 for all features and it was the worst misrecognition rate from among of all class pairs. Among sets of selected features the best was a set consisted of the feature 2 (VCO_2) and 4 (RQ), which gave the global error rate E_r=0.055 and it could good differentiate all possible class pairs. Moreover, the set of all features allowed to diminish the error to 0.050.

Problem which kind of component classifiers ought to be applied deserves for separate consideration. The reasonable approach consists in applying first feature selection and determining the optimum values of *k*'s for the all components classifiers. If values of *k*'s will be larger than two then it is worth to use the fuzzy voting. In the case when k=1 there will be no difference between the crisp and fuzzy voting of the component classifiers. If k=2 then ties are very likely, however, the difference between fuzzy and crisp types of voting can appear. For the analyzed data no difference between the fuzzy and the crisp voting was discovered. The cost of computations for the both types of voting is only slightly higher than for one of these types. Thus, it is worth to run these two versions and then forming the final classifier decision.

In summary, the results of the study demonstrate that acute intermittent hypoxia elicits metabolic response which may be very effectively recognized by each of the proposed classifiers. Only, two features such as CO_2 production (VCO_2) and respiratory quotient ($RQ=VCO_2/VO_2$) are enough to differentiate all class pairs of IH periods with misclassification rate from 0.000 to 0.013, except of distinguishing between the first and the final hypoxic exposure (then it might to use the whole set of features and error rate was equal 0.075). The results concerned the metabolic effects of acute intermittent hypoxia corroborate those of our previous studies about the ventilatory response to acute IH that point to usefulness of the pattern recognition approach in the experimental model studies. Moreover, this approach may be helpful in preparation training procedures in sport and rehabilitation for monitoring and evaluation of effects during and after the proposed IHT program. It seems that the classification methods for differentiation the positive/negative/no effects of intermittent hypoxia on tumor cells and their environment in stimulus-reoxygenation periods might be very useful.

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