Machine Learning Possibilities for Evaluation of Arterial Hypertension Treatment Efficiency in Case Study

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Keywords: Arterial Hypertension, Heart Rate Variability, Machine Learning, Quadratic Discriminant Analysis.

Abstract: The paper aims to discuss questions concerning application of the machine learning based decisions in the area of the clinical diagnostics. In previous works it was shown that it is possible to develop a decision support system based on the most indicative parameters of the short-term heart rate variability signals for the express diagnosing of the arterial hypertension using methods of machine learning. This paper show results of the case-study for analysis of the machine learning based results for evaluating duration of the treatment using the device for the neuro-electrostimulation. Comparative analysis of the results of the quadratic discriminant analysis application and instrumental measurements highlights concern regarding using of a single method in such complex task as a clinical process. Possible limitations and advantages of each method were discussed.

1 INTRODUCTION

It is known that the functional purpose of the autonomic nervous system (ANS) is to maintain a constant internal environment (homeostasis) and provide various forms of mental and physical activity. Autonomic disorders are one of the urgent problems of modern medicine. This is due to several factors, and above all, the enormous prevalence of autonomic disturbances (up to 80% of observations occur). With violations of the ANS, fluctuations in blood pressure are observed in 36% of patients. Arterial hypertension was chosen as a clinical model accompanied by autonomic disorders (da Silva et al., 2014).

An analysis of the pathophysiological factors of arterial hypertension (AH) indicates the exceptional role of the ANS in the formation of AH (Kseneva, Borodulina, Trifonova, & Udut, 2016). One indirect way to assess functioning of the ANS is the evaluation of heart rate variability (HRV) (Baevskiy, 2001). A number of studies claim that the prognostic significance of HRV itself is very moderate. However, in combination with other methods, it becomes even more significant in assessing cardiac mortality and rhythm disturbances. Evaluation of the results of functional tests requires special attention, as their use has serious advantages, since it allows one to minimize individual differences and evaluate the direction of changes (Ushakov, Orlov, Baevskii, Bersenev, & Chernikova, 2013).

In the treatment of hypertension can be used as pharmacological agents and physiotherapy techniques. According to guidelines for hypertension Russian Medical Society of arterial hypertension and Russian Scientific Society of Cardiology, for the treatment of hypertension used a combination of several drugs.

Adverse events in this case may be one of the possible side effects is polypharmacy. Methods of physiotherapy effects can be used both independently and accompanying with a pharmacological drug. Thus during the treatment process usually provided correction of autonomic disturbances aimed to improving the blood circulation system (Mancia et al., 2013). However, far from always in this case the required clinical effect required clinical effect of optimizing the state of the ANS is provided.

In the present work, the results of clinical trials in the treatment of patients with AH are presented. In these studies, used device allowed for application in

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Kublanov, V., Kazakov, Y. and Dolganov, A.
Machine Learning Possibilities for Evaluation of Arterial Hypertension Treatment Efficiency in Case Study.
DOI: 10.5220/0009372004110416
In *Proceedings of the 13th International Joint Conference on Biomedical Engineering Systems and Technologies (BIOSTEC 2020) - Volume 1: BIODEVICES*, pages 411-416
ISBN: 978-989-758-398-8; ISSN: 2184-4305

Russia - to corrector of the sympathetic nervous system activity "SYMPATHOCOR-01". During treatment, the technique of Dynamic Correction of the Activity of the Sympathetic Nervous System (DCASNS) was used (Petrenko, Kublanov, & Retiunskiy, 2015).

Some results of these studies are given in (Darya D. Egorova, Myakotnykh, Kazakov, & Kublanov, 2014), in which 112 patients participated (40 women, 72 men), with an average age of 45.85 ± 12.41 years. These patients suffered from stage II – III AH and had various clinical symptoms of ANS dysfunction. According to the options for the drugs used the patients were comparable in the drug antihypertensive therapy (including angiotensin - converting enzyme inhibitors, diuretics, slow calcium channel blockers). Although the effectiveness of treatment at different periods was ambiguous, which is quite common in patients with hypertension.

When using the "SYMPATHOCOR-01" device, the biotropic parameters of spatially distributed current pulses were selected individually (V. S. Kublanov, 2008). The treatment course consisted of 10 procedures, and during each procedure:

- 5 minutes of the field exposure in the projection of the left upper cervical ganglion of the sympathetic nervous system,
- 5-minute break,
- 5 minutes of the field exposure in the projection of the right upper cervical ganglion.

Therapeutic sessions were on daily basis. During treatment, HRV was recorded in dynamics - before treatment, after the 1st, 5th and 10th procedures of DCASNS.

The data given in (Darya D. Egorova et al., 2014) indicate that during the treatment process normalization of elevated systolic blood pressure was observed after the 1st session of DCASNS and a slight decrease in the level of diastolic blood pressure after the 10th session of DCASNS.

At the same time, the principal component analysis method was used, which allowed the analysis of HRV to identify aggregated factor indicators that are most sensitive to functional changes in the body. So after the 10th treatment procedure, the parameters of the clusters of the main components deteriorate, although, on the other hand, the number of patients in the cluster with the best indicators increases. A similar result, according to the authors, may be due to the fact that when choosing the number of treatment procedures, the individual dynamics of changes in HRV parameters were not taken into account.

It is likely that a decrease in the level of systolic and diastolic blood pressure as a result of the course of DCASNS should not be considered as the only indicator of evaluating the effectiveness of this type of exposure, especially since all patients received individually selected basic treatment with antihypertensive drugs. The reaction of regulatory systems, primarily the ANS, to external therapeutic effects (for example, DCASNS) may have individual differences, which must be taken into account when selecting biotropic parameters of exposure and determining and duration of treatment.

In the work (Vladimir Kublanov & Dolganov, 2019) presented a new method of forming complexes diagnostically significant parameters of the HRV for the diagnosis of AH. A distinctive feature in the formation of these parameters is the application of original algorithms based on the paradigm of evolutionary programming. The formed parameters complexes allow for express diagnostics with high values of accuracy, specificity and sensitivity (98.5, 100.0 and 96.0%, respectively) on the training sample using leave-one-out (LOO) cross-validation technique, and also has the ability to generalize — the diagnostic accuracy is 93.0% on the validation sample.

The objective of this work is to analyze and discuss possibilities of using complexes of diagnostically significant HRV parameters to determine *the optimal number of neuro-electrostimulation procedures*.

2 MATERIALS AND METHODS

2.1 Clinical Trials (Part 1)

Original studies (Vladimir Kublanov & Dolganov, 2019) were conducted for two groups of patients: almost healthy (28 people); and patients suffering from AH II - III degree before treatment (40 people). Data were obtained at the Sverdlovsk Regional Clinical Psychoneurological Hospital for War Veterans (Yekaterinburg). For registration of electrocardiogram and HRV signals, the corresponding recording channel of the "Eencephalan- -131-03" analyzer was used.

The studies of the HRV signals were carried out when performing a passive orthostatic test, and included the state of functional rest (state F), the state of passive orthostatic load (state O), the state of aftereffect (state K). HRV signals in each state were recorded for 5 minutes.

2.2 Significant Parameters

A complete set of parameters includes statistical parameters, geometric parameters, spectral parameters in accordance with the recommendations of the European Society of Cardiology (Malik, 1996) and the Commission for Clinical Diagnostic Instruments and Apparatuses of the Committee on New Medical Technology of the Ministry of Health of the Russian Federation, as well as a set of the most significant non-linear parameters (Sivanantham & Shenbaga Devi, 2014; Tarvainen, Niskanen, Lipponen, Ranta-Aho, & Karjalainen, 2014).

In the present study, in addition to generally accepted parameters, wavelet transform parameters were used (D.D. Egorova, Kazakov, & Kublanov, 2014). A total of 64 disjoint sets of parameters were used in three functional states. Since the parameters in different functional states were considered separately, the total length of the parameter vector was 192.

Studies of assessing the accuracy of diagnosing arterial hypertension using different machine learning methods and different approaches to the formation of complexes of diagnostically significant parameters allowed to establish the following.

The best classification results are achieved using Genetic programming and Quadratic Discriminant Analysis. The maximum classification accuracy (98.5%) using LOO cross-validation was achieved using complexes of diagnostically significant parameters consisting of Statistical (Mean, Heart Rate, Zero-Crossing Rate), Geometric (Stress Index), Spectral (LF/HF ratio, normalized powers of HRV spectral components, maximum frequencies of HRV spectral components), Nonlinear (Entropy), Wavelet (Entropy of time series HF (t), LF (t), VLF (t)) parameters. In this case, the best solution contains parameters registered in all functional states (V. Kublanov, Dolganov, & Gamboa, 2017).

If a quadratic discriminant analysis is used to predict the class of the test subject ("healthy" or "patient suffering from hypertension"), the result of this operation will be the probable class of the test subject and the probability of belonging to this class. Since in our case there are only two classes of subjects, the use of quadratic discriminant analysis allows us to reduce the multidimensional space of diagnostically significant parameters to the one-dimensional space of the metric of the decision rule.

When the classifier is trained, a separating hyperplane is formed, which "separates" the two classes of subjects. In the space of the decision rule, this hyperplane defines the origin. In our case, positive values of the metric in the space of decision rules correspond to the class of subjects "healthy", negative values of the metric correspond to the class of subjects "patients suffering from hypertension".

The table 1 shows combinations of variables determined using genetic programming that have the highest classification accuracy (Vladimir Kublanov & Dolganov, 2019). Combinations are named according to the number of features in them.

Table 1: Best Parameters Combinations.

Name	***ACC, %***	***SPE, %***	***SEN, %***	***Features***
QDA -12	***98,5***	***100***	***96***	F HR F EnInterp O kurtosis O IAB O LF/HF f O LFn wt O SD1/SD2 K IAS K f(LFmax) K SDHF K EnHF K EnVLF
QDA -14-1	***98 5***	***100***	***96***	F SI F EnInterp O kurtosis O ZCR O LF/HF f O RF O f(LFmax) O f(VLFmax) O LFn wt K HR K f(LFmax) K VLFmax K EnHF K EnVLF
QDA -14-2	***98 5***	***100***	***96***	F SI F EnInterp O HR O kurtosis O LF/HF f O RF O f(VLFmax) O LFn wt O EnVLF K f(LFmax) K VLFmax K HF wt K EnHF K EnVLF
QDA -14-3	***98 5***	***100***	***96***	F SI F EnInterp O kurtosis O ZCR O LF/HF f O RF O f(LFmax) O f(VLFmax) O LFn wt O EnVLF K f(LFmax) K VLFmax K EnHF K EnVLF
QDA -15	***98 5***	***100***	***96***	F SI F EnInterp O kurtosis O ZCR O LF/HF f O RF O f(LFmax) O f(VLFmax) O LFn wt O EnVLF K HR K f(LFmax) K VLFmax K EnHF K EnVLF

2.3 Clinical Trials (Part 2)

To evaluate the effectiveness of the obtained combinations of parameters for solving the problem of diagnosing AH and their ability to generalize, a study was conducted on data that was not used for training. This work uses case-study data from 5 patients. In addition to HRV data, blood pressure was measured using professional tonometer. Data were obtained at the Sverdlovsk Regional Clinical Psychoneurological Hospital for War Veterans (Yekaterinburg).

Diagnostic results were obtained for all 5 patients before treatment, after 5 procedures, and after 10 procedures for using the biotechnological system of multichannel neuro-electrostimulation by "SYMPATHOCOR-01" device.

3 RESULTS

The table 2 provides quadratic discriminant analysis decision rule metrics, which show the likelihood of belonging to the particular class for 5 combinations of parameters that have the best estimates of accuracy, sensitivity and specificity in the classification.

The data is provided for signals recorded before (0), after 5 and after 10 procedures of neuro-electrostimulation. The table 3 shows the measurement data of diastolic and systolic blood pressure (BPs and BPd) and heart rate (HR) recorded during the state of functional rest (state F), during the orthostatic test (state O), and for the stage of aftereffect (state K).

Table 2: Machine Learning Results.

Patient	QDA-12	QDA-14-1	QDA-14-2	QDA-14-3	QDA-15
P1 - 0	-10,2	-85,0	-54,6	-66,5	-81,6
P1 -5	18,0	9,9	40,8	28,8	32,6
P1 - 10	2,6	-51,5	-29,1	-20,2	-30,8
P2 - 0	-27,5	-15,4	-22,5	-14,0	-11,2
P2 -5	-33,1	-15,0	-21,7	-12,0	-14,8
P2 - 10	-4,9	-48,5	-32,0	-45,4	-45,0
P3 - 0	-56,6	-71,0	-62,6	-70,9	-70,9
P3 -5	-27,1	-8,2	-20,1	-6,9	-5,2
P3 - 10	-24,5	-65,1	-59,2	-68,7	-72,6
P4 - 0	-50,8	-491,8	-527,8	-522,1	-523,9
P4 -5	-16,9	-142,4	-132,0	-150,1	-150,4
P4 - 10	-23,6	-18,5	-21,5	-18,1	-18,4
P5 - 0	-8,4	-33,6	-42,9	-48,9	-48,7
P5 -5	-8,8	-10,0	-7,5	-11,5	-11,6
P5 - 10	-10,4	-15,4	-12,3	-14,0	-14,4

Table 3: Measurements Results.

	State F			State O			State K		
Patient	BPs	BPd	HR	BPs	BPd	HR	BPs	BPd	HR
P1 - 0	112	57	77	95	63	125	126	63	80
P1 -5	114	53	65	100	69	107	118	67	69
P1 - 10	114	60	84	107	69	116	123	62	78
P2 - 0	129	73	53	121	86	74	129	75	51
P2 -5	132	80	55	123	85	68	124	80	68
P2 - 10	107	66	62	111	83	82	113	66	58
P3 - 0	121	73	70	134	90	79	127	77	75
P3 -5	110	68	61	130	86	82	111	67	64
P3 - 10	112	85	60	128	85	84	114	70	74
P4 - 0	131	75	90	131	86	94	136	77	84
P4 -5	145	79	62	142	83	82	146	82	72
P4 - 10	170	93	62	164	105	70	152	86	66
P5 - 0	95	61	56	97	65	65	90	57	58
P5 -5	92	63	60	91	66	67	91	62	59
P5 - 10	92	65	56	82	65	70	86	60	67

It is worth noting that negative estimates of the likelihood ratio for all patients before the course of treatment indicates the possibility of generalizing the combinations obtained.

Patient 1, after 5 procedures, became defined as healthy (positive value of likelihood ratings). Changes in state can be associated with normalization of heart rate in all stages and stabilization of systolic pressure during an orthostatic test. After 10 procedures, 4 out of 5 combinations evaluate this patient as belonging to a group of patients, which is consistent with blood pressure measurements.

For Patient 2, there is a similar behavior of estimates of combinations of heart rate variability parameters for records before and after 5 procedures, which does not contradict the data of instrumental measurements of blood pressure. An increase (modulo) the likelihood ratio for 4 out of 5 combinations is consistent with a significant decrease in systolic pressure. At the same time, a decrease in the QDA-12 combination score can be associated with normalization of heart rate. Such a phenomenon may indicate the sensitivity of various combinations to various physiological processes.

Patient 3 also has different dynamics of different combinations. According to the QDA-12 combination, there is a dynamics of assessments towards relatively healthy patients, after 5 procedures and maintaining this level after 10 procedures. This is consistent with a change in the nature of fluctuations in the parameters of systolic pressure and heart rate during an orthostatic test. On the other hand, 4 combinations indicate a deterioration after 10 procedures, which is consistent with changes in diastolic pressure.

Patient 4 - normalization of heart rate, which is partly consistent with QDA-12, blood pressure varies greatly.

Patient 5 has underestimated likelihood ratios for 4 of the 5 pre-treatment combinations that are associated with a variation in heart rate and blood pressure during an orthostatic test. After 5 and 10 procedures, estimates based on heart rate variability data change slightly, which corresponds to blood pressure measurements.

4 DISCUSSION

Comparison of the results obtained using a discriminant analysis and the measurement results of blood pressure and heart rate allows to assume a number of conclusions. In fact, there are two "families" of parameters combinations. The first includes a combination of QDA -12, the second includes the remaining parameters (most of the parameters in these combinations are repeated).

First of all, different QDA combinations are consistent with different features of the patients and different functional states. In particelar, QDA-12 combination is most consistent with the change in heart rate recorded in the State F. For this combination, the "most optimal" is a heart rate of about 62-65. Moreover, deviations up and down are equally sensitive for this combination of parameters.

At the same time, other combinations are more sensitive to changes in heart rate when the patients are in States O and K.

The use of HRV as a parameter for assessing the effectiveness of the treatment of arterial hypertension is certainly justified and has well-known advantages. The main one is the possibility of individual selection of treatment depending on the state of autonomic nervous regulation for a particular patient, and the possibility of dynamic control of the *number of treatment procedures*, the effectiveness and safety of the therapy.

However, this approach has several limitations. First, the formation of hypertension is affected by many complex interacting mechanisms (Bajkó et al., 2012). Secondly, the functional state and reactivity of the ANS in hypertension, including the response to exposure to physical factors, may vary depending on the degree and stage of hypertension, the presence and combination of risk factors (smoking, dyslipidemia , overweight) (Banik, 2014), target organ damage (brain, kidneys, blood vessels, heart) (Melillo, Izzo, De, & Pecchia, 2012), the state of the stiffness properties of the vascular wall (including their changes in case of damage to target organs of AH).

It is known that the spectral parameters of HRV (HF, LF, VLF values) can respond to changes in the biochemical composition of blood, including the content of catecholamines, angiotensin II, BDNF, and products of oxidative stress (Allen, Jennings, Gianaros, Thayer, & Manuck, 2015; Ferrario et al., 2015). The psycho-emotional state of the patient has a huge impact on HRV, including the presence, nature and severity of anxiety-depressive spectrum disorders, which are often found in hypertension (Bajkó et al., 2012; Togo, Kiyono, Struzik, & Yamamoto, 2006). The dynamic interaction of these and many other factors, known and not yet fully studied, can change HRV and the ANS response to exposure in patients within one general group, comparable in a number of clinical and biological parameters (age, gender, degree of increase in blood pressure, n stage AH). Therefore, HRV cannot always be used as the only tool for assessing the patient's condition and receiving feedback in the treatment of hypertension.

The search for solutions to this problem can be in the creation of integrated assessment systems (for example, the previously successfully used comparison of HRV parameters and indicators of the blood supply to the brain and the main arteries of the head (according to ultrasound data), a number of laboratory test parameters), duration and mode of exposure to physical factors, identification of key indicators, determining the effectiveness and duration of the course of treatment.

5 CONCLUSIONS

The paper describes case-study of the arterial hypertension treatment using neuro-electrostimulation device “SYMPATHOCOR-01” and its efficiency evaluation using methods of machine learning.

The pathophysiological factors of arterial hypertension indicate the exceptional role of the autonomic nervous system violations. Because of that in previous works was developed the decision support system based on the most indicative parameters of the short-term heart rate variability signals (which are indirect way to assess functioning of the autonomic nervous system) for the express diagnosing of the arterial hypertension using methods of machine learning. In particular, it was shown that original algorithms of the feature selection based on the evolutionary programming paradigm allow to obtain several combinations of heart rate variability parameters which can be used for the express diagnosing of arterial hypertension,

In this study was tested applicability of such approach in task of the treatment efficiency evaluation. Case study was conducted in which the neuro-electrostimulation device “SYMPATHOCOR-01” was used as a method of physiotherapy.

Comparative analysis of the quadratic discriminant analysis application results and instrumental measurements highlights concern regarding using of a single method in such complex task as a clinical process.

The search for solutions to this problem in the creation of integrated assessment systems is an important scientific and practical task.

ACKNOWLEDGEMENTS

The reported study was funded by RFBR according to the research project № 18-29-02052 and supported by Act 211 Government of the Russian Federation, contract № 02.A03.21.0006.

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