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ORIGINAL

DIAGNOSIS OF BRONCHIAL HYPERRESPONSIVENESS IN SPORTSMEN THROUGH THEIR PC_{20} VALUE

DIAGNÓSTICO DE HIPERREACTIVIDAD BRONQUIAL EN DEPORTISTAS MEDIANTE EL VALOR DEL PC20

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ABSTRACT

In this study the criteria of the International Olympic Committee versus the Spanish Society of Pneumology and Thoracic Surgery are exposed.
A study was conducted in eighty high performance athletes of several sports. They underwent a medical history, resting spirometry and a methacholine challenge test. Sensitivity and specificity of methacholine test were analyzed by using Receiver Operating Curves (ROC curves). International anti-doping Committee requires that the decline is with a PC_{20} < 4mg/ml, while for clinical practice this fall must present a PC_{20} < 8mg/ml.

Twenty five percent of the sportsmen studied had a PC_{20} > of 8mg/ml; 61% had a PC_{20} < 4mg/ml; and 14% had between 4 and 8mg/ml PC_{20}. The best cut-off point was found for a PC_{20} of 7.6 mg/ml with a specificity of 98.3 and a sensitivity of 100%.

The same criteria should be determined to diagnose both sportsmen and nonathletes.

KEY WORDS. Bronchial hyperresponsiveness. Trained Athletes. Methacholine Test. PC_{20}.

RESUMEN

En este trabajo se exponen los criterios de positividad del Comité Olímpico Internacional versus a la Sociedad Española de Neumología y Cirugía Torácica.

Participaron en este estudio ochenta deportistas de alto rendimiento, realizando una historia clínica, una espirometría de reposo y un test de metacolina. Se analiza la sensibilidad y especificidad del test de metacolina mediante curvas ROC. El comité Internacional antidopaje (WADA) requiere que la disminución sea con un PC_{20} < a 4mg/ml, mientras que para la práctica clínica este descenso debe presentar un PC_{20} < 8mg/ml.

Los resultados fueron: 25% tuvieron un PC_{20} > de 8mg/ml; el 61% obtuvieron un PC_{20} < 4mg/ml y un 14% presentaron un PC_{20} entre 4 y 8mg/ml, correspondiendo el mejor punto de corte a PC_{20} de 7,6mg/ml con especificidad de 98,3 y sensibilidad de 100%.

Se tendría que determinar los mismos criterios para el diagnóstico de los deportistas y los que no lo son.

INTRODUCTION

The increased use of β_2 agonists among sportsmen in all sporting disciplines promoted the fact that the International Olympic Committee Medical Commission established restrictions in the use of this medication. From the 2002 Winter Olympic Games onwards, especial documentation was requested in order to get a Therapeutic Use Exemption (TUE) approval for its use[1,2]. Sportsmen had to present their case history together with the verification of obtaining a positive result in one of the following bronchial provocation tests: stress test, methacholine test, isocapnic voluntary hyperventilation test and/or bronchodilation test, and from 2009 the results obtained in the mannitol test were also valid. Sportsmen's appropriate treatment is really important, not only to control and prevent symptoms, but also to reduce the effects on their sports performance[3]. 30% of the TUE obtained in Athens 2004 Olympic Games were carried out through a methacholine test[4,5].

In order to carry out an accurate diagnosis of bronchial hyperresponsiveness through the methacholine test, it is necessary to set a cut-off point, since prevalence of this pathology changes among sportsmen. Therefore, the World Anti-Doping Agency (WADA) only accepts the diagnosis of bronchial hyperresponsiveness (BH) if obtained by a methacholine test when the forced expiratory volume in one second (FEV_1) decreases more than 20% and the PC_{20} is ≤ 4 mg/ml. If the sportsman is taking steroids, the PC_{20} allowed during three months is ≤ 6.6mg/ml. According to the Spanish Society for Pneumology and Thoracic Surgery (SEPAR), BH is considered positive if there is 20% decrease of FEV, and Methacholine concentration (PC_{20}) lower than 8 mg/ml. Sportsmen with a PC_{20} between 4 and 8 mg/ml in our clinical sphere would present a diagnosis of bronchial hyperresponsiveness with the appropriate treatment, although if they are under the guidelines of international bodies they will be penalized.

From 1st January 2010 sportsmen were offered the possibility of BH treatment with salbutamol or salmeterol with no restrictions at all. Meanwhile, in order to use terbutaline and formoterol, TUE was required[6-9]. It is well known that the list of forbidden substances and requirements to obtain the TUE are revised by WADA every year and are constantly changing.

The aim of this project was to study the following matters: a) were this project’s sportsmen accurately treated or were they treated above or below treatment threshold?; b) determining bronchial hyperresponsiveness’s prevalence according to WADA and SEPAR’s criteria; c) if WADA requires again TUEs to treat with any bronchodilator, which cut-offs would be the most appropriate to avoid inequality between sportsmen and nonathletes?: d) is this medication beneficial for all sportsmen or only for those who suffer from bronchial hyperresponsiveness?

PATIENTS AND METHODS

This prospective study was carried out in the Andalusian Centre for Sports Medicine in Malaga (CAMD), with the approval of the Ethics Committee of the Andalusian Centre for Sports Medicine, from the Regional Ministry of Tourism, Commerce and Sport of the Junta de Andalucía, under the Declaration of Helsiki’s guidelines. Before the start of this study an informed consent was signed by each individual or by parents or legal guardians of minors.
There were 80 federated sportsmen from different sports participating in this study (Figure 1): 5% were triathlon athletes, 7.6% rowers, 5% canoeists, 48.80% were swimmers, 2.5% practiced weight-lifting and wrestling, 7.5% practiced team sports, 8.6% were cyclists and 15% athletes; all came from high-performance sport programmes at the moment of the study.

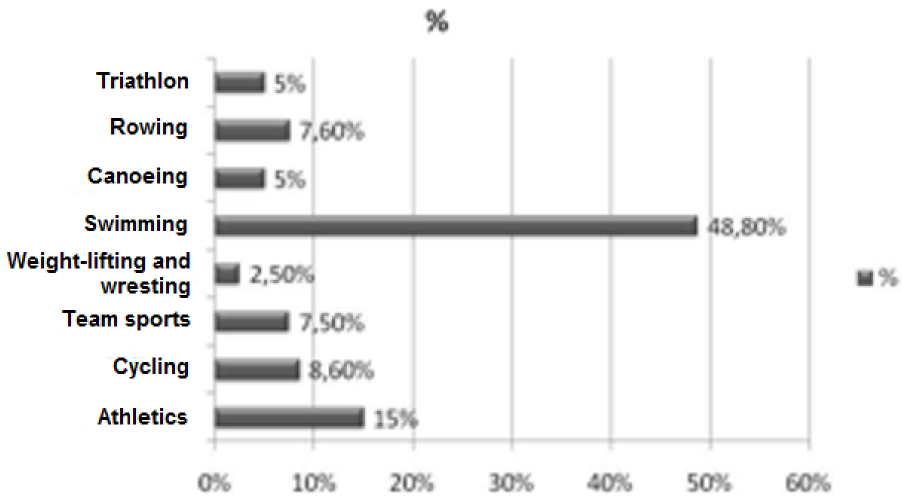

Figure 1.- Percentage of sportsmen from different sports

Sportsmen were recruited from sport clubs in Malaga by sending them an invitation letter to participate in the study and from Malaga's CAMP were sportsmen's medical examination was performed. The inclusion criteria for this study were the following: to be between thirteen and thirty years old, to be federated, to recruit men and women, to belong to a high performance programme, to compete at regional, national or international level and to present shortness of breath during or after exercise. The study was carried out during a year.

Sportsmen included were between thirteen and thirty years old, and the average age was 18 years old. A case history was performed with each participant including their identity papers, gender, age, sport performed, level of competition, family history and personal history with especial attention to asthma and allergies diagnosed, respiratory symptoms and treatments followed for these pathologies. None of them were smokers. Sportsmen should stop their BH treatment from twenty-four to seventy-two hours before carrying out the methacholine test; time depends on the average life of the medicine used.

A physical examination is performed; it includes the following tests:

1) Basic Anthropometry. The measurement of these variables follows the protocol recommended by the Spanish Group of Cineanthropometry[10]. In order to perform the anthropometric analysis scales and a Seca measuring rod (Seca Ltd, Germany) with an accuracy of 1mm.

2) A resting electrocardiogram test was carried out, participants' blood pressure was taken, and inspection, percussion and auscultation of cardiopulmonary apparatus were performed.

3) Then, a forced basal spirometry was performed. Default values were defined according to the SEPAR's[6] recommendations as the best values found after

performing three spirometries. The FEV_1 value obtained in it is the one we take as reference when carrying out the methacholine test in order to obtain the test result (positive or negative).

4) Methacholine Test. A Datospir 120 spirometer and a Hico-Ultrasonat 806 nebulizer were used. Before the test the room's temperature, humidity and pressure were checked with a Termofix thermometer and hygrometer and with a Cyco barometer. Sportsmen has rested at least twelve hours without training before the test. Those participant taking BH treatment had to stop it before the test (24, 48 or 72 hours before the test depending on the average life of the medicine used). Methacholine test was performed according to the protocol of continuous aerosol generator with intermittent inhalations recommended by SEPAR.

Methacholine dilutions were prepared from drug dispensed in powder. With this aim, four dilutions were prepared. In the first one or Medicine Bottle A a hundred milligrams of methacholine were dissolved in two hundreds milliliters of saline solution; the result was a concentration of 5mg/ml. In Medicine Bottle B we put ten milliliters from Bottle A with ten milliliters of saline solution, with the result of a concentration of 2.5mg/ml. In Medicine Bottle C, there were two milliliters from Bottle B together with eighteen milliliters of saline solution, resulting on a concentration of 0.25mg/ml. In Medicine Bottle D, there were teo milliliters from Bottle C and eighteen milliliters of saline solution, obtaining a concentration of 0.025mg/ml. Sportsmen are urged to perform five inhalations. The first one is performed with saline (the results of this first inhalation act as the reference point). These inhalations are followed by each concentration of methacholine, starting with the lowest. Three minutes after finishing inhalations with the lowest concentration the decrease of FEV_1 with regards to the reference point is checked; if the result is positive, i.e. if the decrease of FEV_1 is higher or equal to 20% the test stops, if it is negative, participants continue with concentration in Bottle C following the same method until obtaining a positive result or a negative result with the highest concentration, the concentration corresponding to Bottle A.

Statistical analysis

For the analysis of the data obtained in this study we used both SPSS version 11.0 (SPSS Inc, IL, USA) and MedCal version 7.3 (Mariakerke, Belgium). First, descriptive data on mean, standard deviation, maximum, minimum, and ranges for all variables studied were obtained. After that we determined whether the variables studied were within normal through the Kolmogorov-Smirnov test. Then, the ROC curves were performed to determine sensitivity (proportion of ill sportsmen with a positive test result), specificity (percentage of sportsmen without disease who obtain a negative test result), positive predictive value, negative predictive value and cutoff of PC_{20} values obtained by methacholine test. The Area Under the Curve (AUC) is defined as follows: 0.90 – 1.00 = excellent; 0.80 – 0.90 = good; 0.70 – 0.80 = medium; 0.60 – 0.70 = poor; < 0.60 = very poor.

RESULTS

The characteristics of the sportsmen included in the study are shown in Table 1.

Table 1: Sportsmen's characteristics: average and standard deviation.

	Women (n=32)	Men (n=48)
Size (cm)	163,53 ± 6,20	175,65 ± 7,03
Weight (Kg)	58,28 ± 8,71	71,05 ± 10,14
IMC (Kg/m^2)	21,72 ± 2,34	23,02 ± 2,90
Asthmatic/alergic	0%	21,3%

21.3% of them were diagnosed with asthma, alergy and/or bronchial hyperresponsiveness by their family doctor (through symptomatology) or by their allergist through skin tests. The rest, 63 (78.75%) were healthy.
20% of the studied sportsmen (all previously diagnosed by their doctor) had medication prescribed for this pathology. 15% were taking β2 adrenergic agonists and 5% were using inhaled corticosteroids and β2 adrenergic agonists. From this 5%, 3% were being vaccinated and they had been diagnosed by an allergist. 1.3% had no medication prescribed although they had been previously diagnosed with asthma. It is shown in Figure 2.

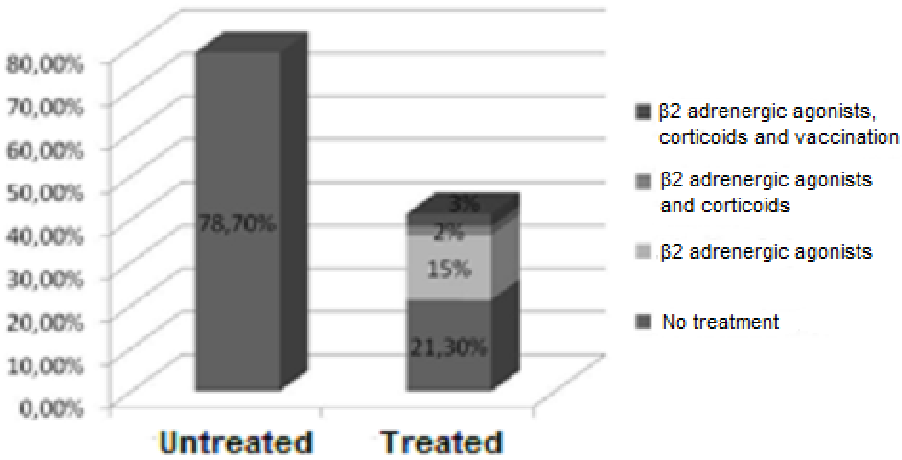

Figure 2.- Sportsmen's treatment

All sportsmen who had been diagnosed with asthma or alergy obtained a positive result in the methacholine test with a PC_{20} < 4mg/ml. 39.7% of the sportsmen not previously diagnosed were diagnosed with bronchial hyperresponsiveness through a bronchial challenge testing, obtaining also a PC_{20} < 4mg/ml. All in all, 61% of the studied sportsmen were positively diagnosed with bronchial hiperresponsiveness with PC_{20} < 4mg/ml. 14% of the sportsmen not previously diagnosed obtained a PC_{20} between 4 and 8 mg/ml; pulmonologists would diagnose them with bronchial hyperresponsiveness while WADA would not. Finally, 25% of those not previously diagnosed presented a PC_{20} higher than 8 mg/ml. (Figure 3)

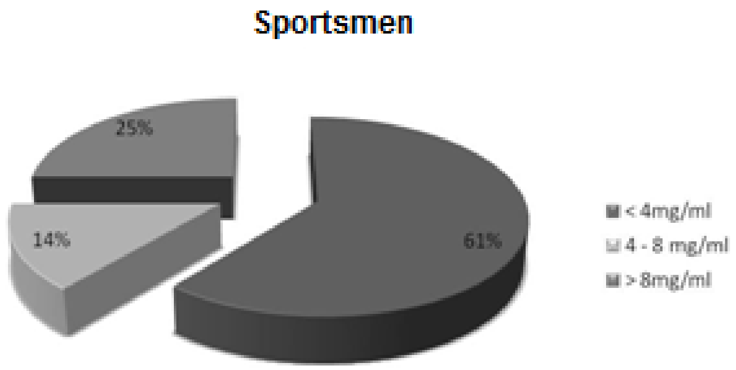

Figure 3.- Percentage of sportsmen according to their PC_{20}

From the eighty methacholine tests carried out, seventy (75%) obtained a positive result and 20 (25%) obtained an objective negative diagnostic test for a methachonile concentration lower than 8 mg/ml. Lung function parameters after having performed the test with sportsmen both with and without bronchial hyperresponsiveness is shown in Table 2.

Table 2: PC_{20}: concentration of methacholine required to decrease FEV_1 by 20% . FVC: forced vital capacity. FEV_1: forced expiatory volume in 1 second. FEF_{25-75}: forced expiratory flow between 25-75%. MEF_{50}: Maximal Expiratory Flow at 50%.

	Positive	**Negative**	**p**
FVC (L)	3.50	4.40	n.s.
FEV_1 (L)	2.70	3.60	p<0.05
FEF_{25-75} (L/s)	2.50	7.90	p<0.05
MEF_{50} (L/s)	270	3.80	p<0.05
PC_{20} (mg/ml)	6.08	14.05	P<0.05

The study of sensitivity and specificity of these data using ROC curves are shown in Table 3. The best cutoff defined as the best sensitivity and the best specificity was for a concentration of methacholine between 4 and 8 mg/ml with a sensitivity of 100% and a specificity of 98.3%, with an area under the curve of 0.99, which means it is excellent.

Table 3: Sensitivity and specificity according to the concentration of methacholine.

	< 4 mg/ml	**4 - 8 mg/ml**	**> 8 mg/ml**
Sensitivity (%)	38.20	100.00	55.60
Specificity (%)	100.00	89.30	100.00
Cutoff	3.90	7.61	14.78
AUC	0.74	0.99	0.82

Standard error, positive predictive value, negative predictive value and negative likelihood ratio are presented in Table 4.

Table 4: Standard error (SE), Positive predictive value (PPV) and Negative predictive value (NPV), and Negative likelihood ratio (-LR) of the concentration of methacholine.

	SE	**PPV**	**NPV**	**-LR**
< 4 mg/ml	0.000	38.2 (29.6- 50.7)	100.0 (92.1-100.0)	0.00
4 - 8 mg/ml	0.001	100.0 (93.7-100.0)	94.7 (74.0- 99.9)	0.01
> 8 mg/ml	0.000	100.0 (69.2-100.0)	86.4 (75.7- 93.6)	0.47

DISCUSION

Under-treatment of asthma in sedentary patients is a very common phenomenon[11,12], but it is not known if sportsmen suffering bronchial hyperresponsiveness are undertreated. The literature[13-15] consulted reported that sportsmen with bronchial hyperresponsiveness are not properly treated. O'Byrne[16] advises to treat bronchial hyperresponsiveness following international protocols in order to avoid under- or over-treatment.

Some studies have shown extensive use of this medication among elite athletes. Helenius[13] studied several Olympic Games and found that there are between 4 and 15% of sportsmen treated of bronchial hyperresponsiveness. Weiler[14] gave a questionnaire to six hundred and ninety nine sportsmen from the Olympic Games in 1996, obtaining as a result that 16.7% of them were taking medication for asthma. Therefore, he concluded that this pathology is more common among sportsmen than in the general population.

Others indicate they are being undertreated, especially if the point of reference is the test for objective diagnosis. Anderson[5] compared the percentage of sportsmen with prescribed treatment for bronchial hyperresponsiveness in the 2000 Olympic Games to those who followed a treatment in the 2004 Olympic Games and he found that the number of sportsmen had decreased, since they had to present an objective diagnostic test of bronchial hyperresponsiveness in order to obtain a Therapeutic Use Exemption approval.

Lund[15] analyzed four hundred and eighteen Danish elite sportsmen from endurance sports through a questionnaire. He showed that these sportsmen were generally undertreated.

Thomas[17] carried out a study with German sportsmen who participated in the 2008 Olympic Games. He found that 17% of them were diagnosed with bronchial hyperresponsiveness. However, only 10% of them were following a treatment, so they were then generally undertreated.

The results obtained in this study are in accordance with the above mentioned: 75% of the sportsmen analyzed were diagnosed through the methacholine test, although only 21.3% of them were following a prescribed treatment; therefore, the percentage of under-treatment is 53.7%.

It is known that β_2 agonists are effective bronchodilator drugs. However, sportsmen should use them occasionally, i.e. only when they have the symptoms, and it is recommended to use preventive therapy the rest of the time. The IOC has observed that there is an extended and bad use of these drugs which cause tolerance to this medication. Recommendations for bronchial hyperresponsiveness treatment among sportsmen are to maintain them controlled in order to ensure the effectiveness of the treatment and to treat them with the lowest effective dosage in order to control their symptomatology[18]. Clark[19] published an article in which, after reviewing both the bibliography and the last decade experience's point of view, he recommends patterns of education and behavior in order to take better control of bronchial hyperresponsiveness and to improve the use of pharmacological treatment. The recommendations are the following: to recognize the signs and symptoms of disease, to know their FEV_1 before starting a training or competition and to limit exposure to agents that cause the disease.

Several studies[20,21] show that bronchial hyperresponsiveness in sportsmen is increasing due to the combination of the rise of ventilation owing to the intensive training and environmental factors[22]. The number of sportsmen with bronchial hyperresponsiveness is likely to increase and do the number of sportsmen under treatment. The use of β2 adrenergics will be controlled by the IOC through doping controls where a maximum of 1600 micrograms of salbutamol every 24 hours will be allowed, and every bad use of these drugs will probably be detected. That has echoes of what happened with pseudoephedrine in 2004, when it was removed from the list of prohibited substances, although it was included again in 2010. We now wonder whether with β2 adrenergics will happen the same and we will have to use an objective diagnostic test in order to use them. In that case, which criteria should be standardized?

1. The prevalence of bronchial hyperresponsiveness according to WADA and SEPAR criteria

TUEs were required to justify treatments using β2 agonists and inhaled corticosteroids amongst elite sportsmen[5, 23-26] until January 2010. Nowadays, in order to use salbutamol and salmeterol this approval is not necessary[8]. In order to use any other medication is it compulsory to present a TUE and to obtain it a positive objective diagnostic test is required. One of those diagnostic tests is the one we use in this study; the methacholine test. However, we have realized that there is a problem regarding the criteria established by this method to obtain a positive result. FEV_1 must decrease more than 20% of the reference value with a concentration lower than 4mg/ml in order to be approved by the IOC. However, according to SEPAR, this concentration must be lower than 8mg/ml. Only the sportsmen whose concentration is lower than 4mg7ml obtain a TUE, which causes a grievance situation amongst sportsmen whose concentration is between 4 and 8mg/ml, since they would be considered to suffer from bronchial hyperresponsiveness if they were not athletes. Following the IOC's criteria, we found that 61% and 14% of them presented a PC_{20} between 4 and 8mg/ml. Therefore, according to SEPAR the prevalence of bronchial hyperresponsiveness is 75% of the studied sportsmen. In the study carried out by Naranjo[27] to sportsmen who had been medically examined in the Andalusian Centre of Sports in Seville (CAMD Sevilla) there was a third part of these sportsmen who could not obtain a TUE because they had a PC_{20} between 4 and 8 mg/ml. The American Thoracic Society (ATS) in its procotol[28] if the year 2000 claims that the best concentration of methacholine in order to diagnose bronchial hyperresponsiveness is of 8mg/ml.

2. Best cut-off points according to PC_{20} in order to obtain a TUE

In this study cut-off points are analyzed through ROC curves obtained in the PC_{20} of the FEV_1 amongst high performance sportsmen. The best one is a concentration of 7.6mg/ml with sensitivity of 100% and specificity of 93.3%. This is in accordance with ATS' protocols.

Bowen[29] studied a group of Australian children and the best cut-off point was in 3.9mg/ml with sensitivity of 86.3% and specificity of 36.4%, but this result was obtained with a 15% decline in FEV_1. 60% of the children presented a PC_{20} lower than 7.8mg/ml.

Godfrey[30] studied asthmatic children and young adults through a methacholine test and a stress test in order to determine the best cut-off points though ROC curves. The best cut-off point was for a PC_{20} of 3.3mg/ml with sensitivity of 92% and specificity of 89%.

Liem[31] carried out a methacholine test and a skin test to six hundred and forty children who were born in 1995. The best cut-off point was found in concentrations lower than 4mg/ml, with sensitivity of 71% and specificity of 69%.

3. Are there benefits in sports performance with the use of bronchodilators for all sportsmen with and without bronchial hyperresponsiveness?

We need to consider whether the use of β2 agonists administered both by inhalation and by therapeutic doses have a clear advantage in competitions.

Carlsen[32] performed a study with sportsmen from endurance sports in which he administered formoterol or placebo an hour before carrying out a maximal exercise stress test which measured ventilation parameters and performed spirometries before and after their exercise and he did not find any change in lung mechanics parameters or in the duration of the test. This author suggests performing an objective bronchoprovocation test in order to diagnose bronchial hyperresponsiveness before recommending a treatment for this pathology. In his opinion, there is a great benefit for diagnosed sportsmen, while it is not good for healthy sportsmen.

Van Baak[33] studied whether a dose of salbutamol before doing sport has an effect on endurance during a stress test. The study was carried out with two tests: one after inhaling placebo and another one after inhaling salbutamol. The results showed that endurance exercise was higher after inhaling placebo.

CONCLUSIONS

The conclusions of this study are the following:

1. In order to perform an accurate treatment positive objective diagnostic tests are required.

2. There should be an agreement between the IOC and Pneomological Societies to determine the most accurate criteria to diagnose bronchial hyperresponsiveness so that it does not continue being a restriction opposite to regulations for sportsmen.

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