MEDWIN PUBLISHERS
Committed to Create Value for Researchers

International Journal of Zoology and Animal Biology
ISSN: 2639-216X

Red Blood Cell Distribution Width in Brachycephalic Dogs with Brachycephalic Obstructive Airway Syndrome

Erjavec V and Nemec Svete A*

University of Ljubljana, Veterinary Faculty, Small Animal Clinic, Gerbičeva 60, 1000 Ljubljana, Slovenia

***Corresponding author:** Alenka Nemec Svete, University of Ljubljana, Veterinary Faculty, Small Animal Clinic, Gerbičeva 60, 1000 Ljubljana, Slovenia, Tel: +38614779290; Email: alenka.nemecsvete@vf.uni-lj.si

Research Article

Volume 4 Issue 1

Received Date: December 23, 2020

Published Date: January 12, 2021

DOI: 10.23880/izab-16000263

Abstract

Brachycephalic dogs, such as English and French Bulldogs, Pugs, and Boston Terriers, are prone to a conformation-related respiratory disorder known as brachycephalic obstructive airway syndrome (BOAS). Due to its systemic consequences, BOAS should be considered as a systemic disease. The present study aimed to investigate the red blood cell distribution width (RDW) in BOAS patients with different degrees of BOAS and non-brachycephalic dogs. The latter served as a control group. Red blood cell distribution width is a variable included in the complete blood count report. It is calculated as the coefficient of variation of red cell volume and thus provides the information about the variability in the size of the circulating red blood cell population. Red blood cell width has traditionally been used for differential diagnosis of anemias; however, it has become an important parameter with multiple clinical applications. It is also considered a biomarker of chronic hypoxemia. We included 72 patients with BOAS and 24 non-brachycephalic dogs. According to the severity of the disease, BOAS patients were classified into grade 1 (13 dogs), grade 2 (27 dogs) and grade 3 (32 dogs). Red blood cell distribution width was significantly ($p < 0.05$) higher in all groups of BOAS patients compared to the group of non-brachycephalic dogs. However, we found no significant difference when comparing RDW among the three groups of BOAS patients. Our study showed that BOAS patients had increased variability in red blood cell size compared to controls. Further studies are needed to determine the potential utility of RDW in BOAS and to clarify the role of RDW in BOAS patients in relation to BOAS severity and in relation to cardiovascular risk.

Keywords: Brachycephalic Dogs; Brachycephalic Obstructive Airway Syndrome; Red blood cell Distribution Width; Hematology; Platelets

Introduction

In recent years, brachycephalic dogs have become increasingly popular, possibly due to the similarity between the head shape of brachycephalic dogs and that of human infants. Brachycephalic dogs, such as English and French Bulldogs, Pugs and Boston Terriers, belong to a group of breeds characterized by a severe shortening of the muzzle and thus the underlying bones, as well as a more modest shortening and widening of the skull. Brachycephalic dogs are prone to a conformation-related respiratory disorder known as brachycephalic obstructive airway syndrome (BOAS) [1-6]. Breeding selection for extreme brachycephaly has resulted in the deformation of the upper airway tract leading to obstruction as soft tissues have not reduced proportionally with the length of the skull. Affected dogs show clinical signs that may include inspiratory dyspnea, snoring, stertor and stridor, panting, stress, exercise and heat intolerance, cyanosis, and even syncopal episodes, respiratory distress, gastrointestinal problems, and

disturbed sleep patterns [3-7]. Brachycephalic dog breeds may have additional systemic complications [1]. Even when systemically healthy, these dog breeds were shown to have hypertension and significantly higher packed cell volume and arterial pCO2 and significantly lower arterial pO2 in comparison to non-brachycephalic breeds [8]. Furthermore, hypomagnesemia [9] and hypercoagulability [10] have also been demonstrated in clinically healthy Bulldogs. In addition, the presence of a hypercoagulable state [11] and elevated levels of inflammatory markers [12], and higher levels of cardiac troponin I have been reported in canine patients with BOAS [13].

Brachycephalic obstructive airway syndrome shares features of obstructive sleep apnea syndrome (OSAS) [14,15], which is the most common form of sleep-disordered breathing in humans [16]. Obstructive sleep apnea syndrome is caused by the repetitive collapse of the narrow upper airway during sleep. Patients with OSAS experience repeated episodes of cessation of breathing, leading to hypoxia and reoxygenation, which can cause increased formation of reactive oxygen species/reactive nitrogen species (ROS / RNS) and thus oxidative stress. The latter may further lead to endothelial dysfunction, vascular inflammation and atherosclerosis, which plays an important role in the progression of cardiovascular disease in OSAS patients [16,17].

Increased values of red blood cell distribution width (RDW) [18,19] and an association between RDW and OSAS severity have been reported in OSAS patients with and without cardiovascular disease [19-21]. Red blood cell distribution width has traditionally been used for differential diagnosis of anemias; however, it has become a parameter with multiple clinical applications [22]. It is also considered as a biomarker of chronic hypoxemia [23]. Red blood cell distribution width, an index of red blood cell morphology, is one of the variables included in the complete blood count, so its cost is negligible. It is calculated as the coefficient of variation of cell volume and thus provides information about the variability in the size of the circulating red blood cell population. In addition, RDW is associated with several serious diseases, including most of those that cause hypoxemia [23]. Red blood cell distribution width has been shown to respond to applied hypoxia [22,23]. Intermittent hypoxia, which also occurs in OSAS and BOAS patients, stimulates the synthesis and secretion of erythropoietin, which is one of the factors with great impact on the increase of RDW [22-24]. The RDW has not been reported in BOAS patients. Therefore, our study aimed to evaluate the RDW in canine patients with different grades of BOAS admitted to the Small Animal Clinic for surgical treatment of BOAS.

Material and Methods

A total of 72 client-owned dogs diagnosed with BOAS and 24 healthy dogs of non-brachycephalic breeds undergoing elective surgery were studied. The 24 healthy dogs served as controls. These dogs were considered healthy based on normal history, normal clinical examination, and results of hematological and biochemical analyzes.

At initial presentation, the history of the BOAS patients was obtained using a questionnaire about behavior, health, and lifestyle. All dogs that showed signs of concurrent disease or had received any type of therapy or vaccination within the last month were excluded from the evaluation. A preoperative owner questionnaire to investigate a wide range of clinical signs, i.e., respiratory signs, gastrointestinal signs, exercise tolerance, and sleep disorders, was completed for each dog with BOAS.

The diagnosis of BOAS was based on clinical signs of upper airway obstruction and anatomical anomalities, as described elsewhere [4,25]. The severity of the disease was classified based on the anatomical anomalities of the airway. Patients were classified as grade 1, grade 2, and grade 3 based on the decrease in the radius of the airway at the level of the nasopharynx, oropharynx, laryngopharynx, and larynx after soft palate surgery. Grade 1 patients had no or very mild narrowing of the airways, grade 2 patients had 50% decrease in airways radius and grade 3 patients had almost complete airway obstruction at the level of nasopharynx, oropharynx, laryngopharynx and larynx. The patients with BOAS were scheduled for surgical treatment under general anesthesia. The patients' health status was assessed by history, physical examination, and blood tests including complete blood count with white blood cell differential count (only results on RDW are shown in this manuscript), serum biochemical analyzes (data not shown), and blood gas analyzes (data not shown).

Formal written consent was obtained from the owner. All procedures complied with the relevant Slovenian governmental regulations (Animal Protection Act UL RS, 43/2007). The study was evaluated and approved by the Ethical Committee on Animal Research of the Veterinary Faculty, University of Ljubljana. Hematological analyzes were performed within one hour after collection of blood samples using an automated laser-based hematology analyzer (ADVIA 120, Siemens, Munich, Germany) and multispecies software. Data were analyzed using commercial software (IBM SPSS 25.0, Chicago, Illinois, USA). The Shapiro-Wilk test was performed to test whether the data were normally distributed. According to the results of normality tests, non-parametric tests (Kruskal-Wallis test followed by multiple

comparisons and Mann-Whitney test) were used to compare the parameters between the dog groups. The significance level was set at 5%.

Results

The demographic data of the brachycephalic and non-brachycephalic dogs are shown in Table 1. There were no significant differences in weight between non-brachycephalic dogs and BOAS patients; however, patients in BOAS grade 3 were significantly older than control dogs and patients in BOAS grade 1.

Number	Control	Grade 1	Grade 2	Grade 3	All BOAS patients
	24	13	27	32	72
Sex (F/M)	13/11	6/7	16/11	21/11	44/28
Age (months) Median (IQR)	15.0	13.0	31.0	35.0*	30.5
	(11.0 – 40.5)	(8.5 – 28.5)	(16.0 – 55.0)	(19.3 – 67.5)	(16.4 – 55.8)
Weight (kg) Median (IQR)	10.8	8.5	10.1	10.0	10.8
	(7.8 – 22.7)	(6.5 – 12.1)	(8.8 – 12.6)	(8.4 – 11.6)	(8.4 – 11.8)
Breeds	Non-brachycephalic	7 FB, 4 Shih Tzu 1 EB, 1 BST	13 FB, 6 BST, 6 P, 1 EB, 11 Shih Tzu	17 FB, 8 P, 6 BST, 1 Shih Tzu,	37 FB, 14 P, 13 BST, 6 Shih Tzu, 2 EB

*grade 3 patients significantly older than grade 1 (p = 0.010) and control dogs (p = 0.016)
IQR: interquartile range; F: female; M: male; FB: French Bulldog; EB: English Bulldog; P: Pug; BST: Boston Terrier.
Table 1: Demographic data of brachycephalic dogs with various grades of brachycephalic obstructive airway syndrome (BOAS) and healthy non-brachycephalic dogs (Control).

Regardless of BOAS grade, French Bulldogs were the most common breed. These dogs accounted for 37 of the 72 cases.

Red blood cell distribution width was significantly higher in all groups of BOAS patients (Table 2) compared to the group of non-brachycephalic dogs. On the other hand, we found no significant difference when comparing the RDW between the three groups of BOAS patients.

Group	RDW (%) Median; IQR	P values*
Reference range[a]	11.9 – 14.5	
Control (n = 24)	12.5; 12.1 – 13.1	
Grade 1 (n = 13)	13.0; 12.9 – 14.0	P = 0.037
Grade 2 (n = 27)	13.4; 13.1 – 13.9	P < 0.001
Grade 3 (n = 32)	13.1; 12.7 – 13.6	P = 0.027
All BOAS patients (n = 72)	13.2; 12.9 – 13.8	P < 0.001

[a]Hematology analyzer Advia 120 (Siemens, Munich, Germany); *P values indicating the significant difference in comparison to control dogs; n, number of dogs
Table 2: Red blood cell distribution width (RDW) of brachycephalic dogs with various grades of brachycephalic obstructive airway syndrome (BOAS) and healthy non-brachycephalic dogs (Control).

Discussion

In this study, RDW was investigated in brachycephalic dogs with different grades of BOAS. Our results cannot be compared with the results of similar studies conducted in BOAS patients because no papers have been published. Therefore, our results were discussed with the results obtained in OSAS patients since the two syndromes are similar [14,15].

The results of our study showed significantly higher RDW in all grades of BOAS patients compared to non-brachycephalic dogs, although the median values remained within the reference range. These results suggest that BOAS patients have greater variability in the size of red blood cells compared to controls. Similar results were obtained in OSAS patients [18,19]. The higher RDW values in BOAS patients may be due to increased erythropoietin synthesis, as a consequence of the hypoxemia present in these patients [8,14,15]. In addition, a high RDW value in BOAS may be due to other factors, such as inflammation [19,26]. Intermittent hypoxia is one of the important factors that cause systemic inflammation [27]. In BOAS patients, plasma concentrations of pro-inflammatory (tumor necrosis factor alpha) and anti-inflammatory cytokines (interleukin-10, interleukin-13) and nitric oxide were significantly higher than in control dogs and appeared to be related to disease severity [12].

Some limitations must be considered when interpreting our results. The most important limitation of our study is the lack of erythropoietin measurements. The latter would help us in the conclusion of our study. The next limitation is the fact that the patients in BOAS grade 3 were significantly older than the control dogs and patients in BOAS grade 1 and that more of the BOAS patients were female.

Conclusion

Our study showed that BOAS patients had increased variability in red blood cell size compared to controls. Further studies are needed to determine the potential utility of RDW in BOAS and to clarify the role of RDW in BOAS patients in relation to BOAS severity and in relation to cardiovascular risk.

Conflict of Interest

None

Acknowledgment

The authors acknowledge the financial support of the Slovenian Research Agency; (research program P4-0053).

References

1. Meola SD (2013) Brachycephalic airway syndrome. Top Companion Anim Med 28: 91-96.

2. O'Neill DG, Jackson C, Guy JH, Church DB, McGreevy PD, et al. (2015) Epidemiological associations between brachycephaly and upper respiratory tract disorders in dogs attending veterinary practices in England. Canine Genet Epidemiol 2: 10.

3. Packer RM, Hendricks A, Tivers MS, Burn CC (2015) Impact of Facial Conformation on Canine Health: Brachycephalic Obstructive Airway Syndrome. PLoS One 10: e0137496.

4. Dupre G, Heidenreich D (2016) Brachycephalic Syndrome. Vet Clin North Am Small Anim Pract 46(4): 691-707.

5. Fasanella FJ, Shivley JM, Wardlaw JL, Givaruangsawat S (2010) Brachycephalic airway obstructive syndrome in dogs: 90 cases (1991-2008). J Am Vet Med Assoc 237(9): 1048-1051.

6. Liu NC, Troconis EL, Kalmar L, Price DJ (2017) Conformational risk factors of brachycephalic obstructive airway syndrome (BOAS) in pugs, French bulldogs, and bulldogs. PLoS One 12(8): e0181928.

7. Roedler FS, Pohl S, Oechtering GU (2013) How does severe brachycephaly affect dog's lives? Results of a structured preoperative owner questionnaire. Vet J 198(3): 606-610.

8. Hoareau GL, Jourdan G, Mellema M, Verwaerde P (2012) Evaluation of arterial blood gases and arterial blood pressures in brachycephalic dogs. J Vet Intern Med 26(4): 897-904.

9. Mellema MS, Hoareau GL (2014) Hypomagnesemia in brachycephalic dogs. J Vet Intern Med 28(5): 1418-1423.

10. Hoareau G, Mellema M (2015) Pro-coagulant thromboelastographic features in the bulldog. J Small Anim Pract 56(2): 103-107.

11. Crane C, Rozanski EA, Abelson AL, deLaforcade A (2017) Severe brachycephalic obstructive airway syndrome is associated with hypercoagulability in dogs. J Vet Diagn Invest 29(4): 570-573.

12. Rancan L, Romussi S, Garcia P, Albertini M, Vara E, et al. (2013) Assessment of circulating concentrations of proinflammatory and anti-inflammatory cytokines and nitric oxide in dogs with brachycephalic airway obstruction syndrome. Am J Vet Res 74(1): 155-160.

13. Planellas M, Cuenca R, Tabar MD, Bertolani C, Poncet C, et al. (2012) Evaluation of C-reactive protein, haptoglobin and cardiac troponin 1 levels in brachycephalic dogs with upper airway obstructive syndrome. BMC Vet Res 8: 152.

14. Hendricks JC, Kline LR, Kovalski RJ, O'Brien JA, Morrison AR, et al. (1987) The English bulldog: a natural model of sleep-disordered breathing. J Appl Physiol (1985) 63(4): 1344-1350.

15. Hendricks JC (1992) Brachycephalic airway syndrome. Vet Clin North Am Small Anim Pract 22(5): 1145-1153.

16. Eisele HJ, Markart P, Schulz R (2015) Obstructive Sleep Apnea, Oxidative Stress, and Cardiovascular Disease: Evidence from Human Studies. Oxid Med Cell Longev 2015: 608438.

17. Lavie L (2015) Oxidative stress in obstructive sleep apnea and intermittent hypoxia--revisited--the bad ugly and good: implications to the heart and brain. Sleep Med Rev 20: 27-45.

18. Ozsu S, Abul Y, Gulsoy A, Bulbul Y, Yaman S, Ozlu T (2012) Red cell distribution width in patients with obstructive sleep apnea syndrome. Lung 190(3): 319-326.

19. Leon Subias E, Gomara de la Cal S, Marin Trigo JM (2017)

Red cell distribution width in obstructive sleep apnea. Arch Bronconeumol 53(3): 114-119.

20. Sokucu SN, Ozdemir C, Dalar L, Karasulu L, Aydin S, et al. (2014) Complete blood count alterations after six months of continuous positive airway pressure treatment in patients with severe obstructive sleep apnea. J Clin Sleep Med 10(8): 873-878.

21. Morell-Garcia D, Toledo-Pons N, Sanchis P, Bauça JM, Sánchez JM, et al. (2020) Red cell distribution width: a new tool for the severity prediction of sleep apnoea syndrome in children. ERJ Open Res 6(4): 00278-2019.

22. Salvagno GL, Sanchis-Gomar F, Picanza A, Lippi G (2015) Red blood cell distribution width: A simple parameter with multiple clinical applications. Crit Rev Clin Lab Sci 52(2): 86-105.

23. Yčas JW (2017) Toward a Blood-Borne Biomarker of Chronic Hypoxemia: Red Cell Distribution Width and Respiratory Disease. Adv Clin Chem 82: 105-197.

24. Li Y, Li M, Teng Y, Zhang C, Liu Q, et al. (2018) The association between red cell distribution width, erythropoietin levels, and coronary artery disease. Coron Artery Dis 29(1): 74-80.

25. Hedlund CS (2007) Surgery of the upper respiratory system. In: Fossum TW, et al. (Eds.), Small animal surgery. Mosby, St.Luis, USA, pp: 817-866.

26. Lippi G, Targher G, Montagnana M, Salvagno GL, Zoppini G, et al. (2009). Relation between red blood cell distribution width and inflammatory biomarkers in a large cohort of unselected outpatients. Arch Pathol Lab Med 133(4): 628-632.

27. Dewan NA, Nieto FJ, Somers VK (2015) Intermittent hypoxemia and OSA: implications for comorbidities. Chest 147(1): 266-274.