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Effects Of Phlebotomy On Blood Viscosity In Canines With Elevated Hematocrit Levels

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Abstract:
Objective: *The objective of this study was to evaluate the effects of phlebotomy on whole blood viscosity [WBV] and hematocrit [HCT] levels in beagle dogs with initially high measurements, and to assess the physiological responses following phlebotomy.*
Materials and Methods*: Ten neutralized beagle dogs, uniformly raised, were used for this study. The dogs were divided into two groups based on their HCT values: those with values above 50% and those below. We measured WBV and HCT before and after phlebotomy and monitored C-reactive protein [CRP] levels to assess inflammatory responses. Further, we observed changes in fibrinogen levels and other hematological parameters post-phlebotomy.*
Results: *Phlebotomy significantly altered WBV and HCT values in dogs with initially high levels, but not in dogs within normal HCT ranges. No significant change in CRP levels indicated that the procedure did not induce inflammation. Notably, a rapid decrease in HCT was observed within 24 hours post-phlebotomy, accompanied by splenic contraction and subsequent erythropoiesis. Fibrinogen levels initially increased, contributing to the restoration of WBV. By the seventh day, both fibrinogen and WBV had returned to near baseline levels.*
Conclusion: *Phlebotomy significantly impacts WBV and HCT in dogs with elevated levels, with minimal inflammatory response. The body quickly adapts through splenic contraction and erythropoiesis, with fibrinogen playing a key role in restoring blood viscosity. This study highlights the importance of WBV and HCT in clinical assessments and the adaptive physiological mechanisms following therapeutic phlebotomy.*
Key Word*: Whole Blood Viscosity, Phlebotomy, Hemorheology*.

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I. Introduction

Blood tests for hematological and serum chemicals that we currently use are important to diagnose certain diseases and conditions. They also help to examine the functioning of organs and provide information about how well treatments are working [1]. However, since the establishment of guidelines for the use of these tests are from repetitive experiments, [2] and vascular diseases including hyperviscosity syndrome, atherosclerosis, and metabolic syndromes such as hyperglycemia cannot be recognized using these general blood tests, the substitution methods is necessary. Rheology is a scientific field that deals with the flow and deformation behavior of materials, which can be solids, fluids, or gases [3]. Whole blood viscosity [WBV], which is representative of rheology, is useful for diagnosing the aforementioned vascular diseases and is valuable for determining hematocrit [HCT], plasma proteins, shear rate, and morphological changes of red blood cells including aggregation and deformability [4–8]. WBV is produced by the resistance of blood flow and is described by blood thickness and stickiness. Unlike water, it changes with the blood flow in blood vessels because blood has characteristics of a non-Newtonian fluid. Non-Newtonian fluid can be explained as the viscosity in which a fluid can resist gradual deformation caused by shear rate or tensile stress. The distinctive feature of blood means that as the WBV increases, the heart eventually needs more power than usual to supply oxygen or nutrients to the organs and tissues. For these reasons, WBV may provide important diagnostic information about circulatory diseases including cardiovascular disease, dehydration, and hypertension [3, 9–13]. The change in WBV means that vasoactive factors, such as vasoconstrictors and vasodilators, and pro-coagulants are not released due to endothelial dysfunction as well as changes in contents such as HCT and plasma protein. These abnormal WBVs can lead to diabetes, cerebrovascular disease, and secondary renal failure [14]. If the HCT value is within the reference range and the WBV is high, there are no such problems [15]. However, if the HCT is in the state of absolute polycythemia and there is high viscosity, phlebotomy, fluid therapy, or a combination of these methods is needed. As a result, we recommend that WBV measurements should be made before the disease occurs if the individual has a high HCT value. Phlebotomy is a method commonly applied to patients with respiratory failure due to polycythemia and chronic

obstructive pulmonary disease [16]. Phlebotomies can contribute to unfavorable effects including extreme stress, hypovolemic shock, and anemia. Considering this fact, in one study with healthy dogs, one quarter of the routine phlebotomy volume was removed for four weeks, and clinical signs, body weight, and hematological and serum biochemical analytes were analyzed [17]. As far as we know, there is no study that investigates how post-phlebotomy viscosity and associated values change and return to normal levels and the influence of phlebotomies on viscosity when HCT and WBV are high. Therefore, the aim of this study was to identify the effects of phlebotomies on the viscosity and associated values in dogs with high values of HCT and WBV.

II. Material And Methods

Experimental Animals

The experiment was conducted using 10 healthy beagles certified by IACUC. They were castrated if male or spayed if female. The average weight of the dogs was approximately 11.7 ± 1.3090 kg [range = 10.3 to 14.3 kg]. The dogs were raised in a controlled environment and received the same amount of food that was administered at the same time each day. Each dog underwent phlebotomy to identify changes in WBV. In addition, hematology values including RBC , HCT, and HGB and chemistry values including TP, globulin, fibrinogen, and C-reactive protein [CRP] were measured. Among these, according to the HCT values before the phlebotomy, the experimental groups were first classified into two groups. One group was composed of individuals with HCT values greater than 50, and the group had HCT values within the reference range. These two large groups were again divided into five groups according to time period in which the dependent variables were measured: just before the phlebotomy, immediately after the phlebotomy, and 1 day after, 7 days after, and 2 weeks after the phlebotomy. All the blood tests were performed at each time point. CRP, which is a numerical value related to inflammation and a parameter of blood viscosity, was 10 or less before the phlebotomy, and it did not rise 1 day immediately after the blood phlebotomy, thus, it was not measured again.

Blood Sample Collection

The blood [5 ml] for each blood test was collected from the jugular vein. The blood phlebotomy was also performed using the same vein and as much as 30 ml immediately after the first 5 ml blood collection. For the phlebotomy, a 19 or 21 gauge butterfly catheter was used with minimal restraint [18, 19]. Then, 5 ml of blood for the post-phlebotomy tests was collected. The blood samples were transferred to three standard tubes. One tube was coated with EDTA, which was used to determine WBV and blood cell count [CBC] values. The second was an SSGT tube for the chemistry analyzes, and the third was a citrate-coated tube for the plasma fibrinogen analysis, which had significant effects on the results of this experiment. The value of CBC in the blood sample was measured immediately because it could be influenced by blood coagulation. The plain tube for the chemistry analyzes was centrifuged at 3,500 rpm for 10 min at 4 °C. The separated serum was used for the chemistry testing and CRP. The citrate-coated tubes for the plasma fibrinogen were also centrifuged under the same conditions and the plasma was stored at −70 °C until the values were obtained.

Whole Blood Viscosity Analysis

WBV [cP] was measured using a U-shaped scanning capillary-tube viscometer [BVD-PRO1, Bio-Visco, Inc., Republic of Korea]. Unlike other viscometers, viscosity and yield stress can be obtained over a whole range of shear rate from 1 to 1000 s-1. This is a new kind of capillary tube viscometer, and it calculates viscosity using a Casson fluid model.

Hematological Analysis

The CBC was measured using an automatic blood cell counter [Vet ABC, ABX Diagnostics, Montpellier, France]. The red blood cell count [RBC, 106/mm3], white blood cell count [WBC, 103/mm3], hemoglobin concentration[HGB, g/dl], hematocrit[HCT, %], platelet[PLT, 103/mm3], mean corpuscular volume[MCV, um3], and mean cell hemoglobin concentration[MCHC, g/dl] were measured.

Serum Chemical Analysis

For the serum chemistry analysis, WBV-related and other values, which are described below, were measured using an automatic chemistry analyzer [BS-330E, China]. The concentrations of total protein [TP, g/dl], cholesterol [CHOL, mg/dl], phosphorus [P, mg/dl], amylase [AMY, U/L], albumin [ALB, g/dl], and globulin [GLOB, g/dl] were related to the aforementioned viscosity. And the concentrations of alkaline phosphatase [ALP, U/L], alanine transaminase [ALT, U/L], and total bilirubin [TBIL, mg/dl] were the others.

C-Reactive Protein

CRP [mg/l], an inflammatory product known as a secondary factor in viscosity, was obtained from a portable magnetic permeability-based analyzer [LifeAssays Veterinary Reader, LifeAssays AB, Lund, Sweden].

Fibrinogen

Using the Clauss clotting method [STAR evolution, Diagnostica Stago, Asnieres sur Seine, France], the concentrations of fibrinogen [mg/dl] were measured.

Phlebotomy

A Phlebotomy is recommended when there is patient with absolute polycythemia or a high value of WBV, and the amount of blood that is normally withdrawn depends on the weight and the degree of packed cell volume [PCV] . According to the 10% rule, the blood volume generally corresponds to 10% of the animal's body weight, and 10% of this is the total blood volume. In this experiment, assuming that 1.5% of the animal's body weight was 15% of the total volume and considering that the mean body weight was 11.7 kg, 172.5 ml of blood was removed. However, the object of this experiment was not actually polycythemia and considering the unfavorable effects such as hypovolemic shock and anemia after phlebotomy, the amount removed at one time was approximately one quarter of this value. Therefore, we removed a total of 40 ml of blood that include 10 ml for blood analysis before and after the phlebotomy and 30 ml for the phlebotomy.

Statistical Analysis

To find correlations between HCT and WBV before the phlebotomy, a Pearson's correlation analysis was used. WBV, CBC, serum chemistry, CRP, and fibrinogen were analyzed, and an ANOVA analysis was used to determine the significance of these changes at each of the five points. SPSS 18.0.0 [PASW Statistics; IBM Co., Armonk, NY, USA] and GraphPad Prism 5.0 [GraphPad Software, Inc., San Diego, CA, USA] were used for the statistical analyzes. If the p value was less than 0.05, it was considered statistically significant.

III. Result

Value of HCT before phlebotomy

Considering that the Mean and standard deviation of HCT in healthy beagle is 44.7 ± 4.2, 10 beagles was classified into 2 groups : group 1 close to the upper limit that is bigger than 50 and the group 2 with under the value 50 [20]. Five healthy dogs were in each group, the average HCT of the group 1 was 58.8 and the group 2 was 49.68

Correlation between HCT and WBV before phlebotomy

HCT was statistically correlated with WBV at SR 1 s-1 and SR 300 s-1, and they were illustrated using scatter diagram in figure 1.

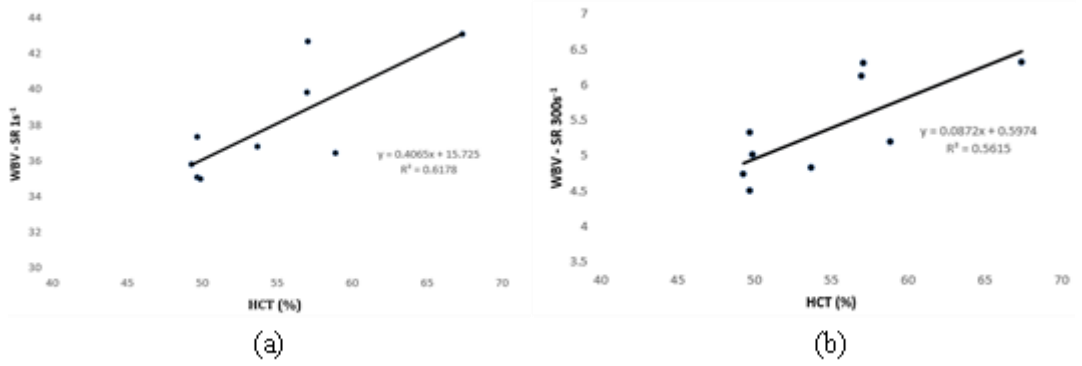


Figure 1. Scatter diagram with r2 values between blood viscosity in diastolic (shear rate 1 s-1) and HCT(a), systolic (shear rate 300 s-1) and HCT(b).

Values of WBV over five points in each groups

The average and standard deviation of the WBV for each of the five points were obtained and are shown in table 1. There is a shear rate which is determined by the diameter of the blood vessel wall and the velocity of blood flow. In this table only shear rate 1 and 300 s-1 representing values of systolic, diastolic and aorta and capillary are represented [5, 21]. Based on that, the changes in WBV is shown in the figure 2 for the group 1 and in 3 for the group 2.

Total group	Time point	Shear rate 1s	Shear rate 300s
Whole Blood Viscosity of Group 1	Before Phlebotomy	39.744 ± 3.1508	5.754 ± 0.6955
	Immediately after Phlebotomy	36.792 ± 5.2693	5.298 ± 0.6635
	24 hours after phlebotomy	24.738 ± 6.2538	3.928 ± 0.5738
	7 days after phlebotomy	38.718 ± 9.4922	5.584 ± 1.0992
	14 days after phlebotomy	36.216 ± 6.1075	5.192 ± 0.7880
Whole Blood Viscosity of Group 2	Before Phlebotomy	37.242 ± 3.4252	5.106 ± 0.5695
	Immediately after Phlebotomy	36.136 ± 2.4856	5.238 ± 0.3737
	24 hours after phlebotomy	31.572 ± 4.3688	4.766 ± 0.4037
	7 days after phlebotomy	34.334 ± 4.3889	4.886 ± 0.6130
	14 days after phlebotomy	34.278 ± 5.1088	4.886 ± 0.5084

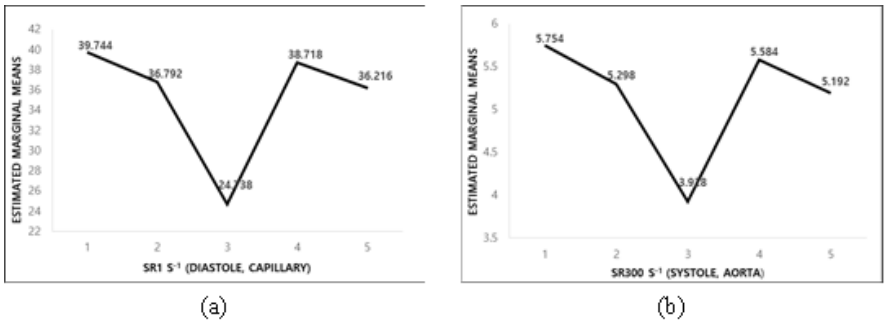


Figure 2. Changes in mean WBV (cP) at shear rate 1 s-1(a) and 300 s-1(b) (group 1).

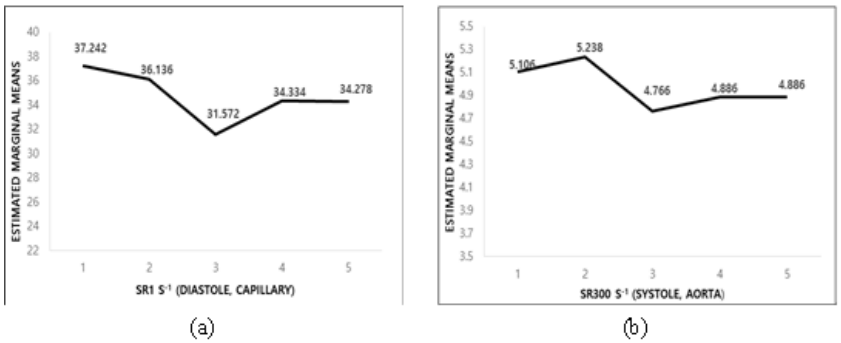


Figure 3. Changes in mean WBV (cP) at shear rate 1 s-1(a) and 300 s-1(b) (group 2).

Values of Hct at five points for each groups.

Mean and SD values of HCT were obtained also at five points for each groups. Following graphs show changes of mean HCT[%] and SD values which are illustrated in Figure 4.

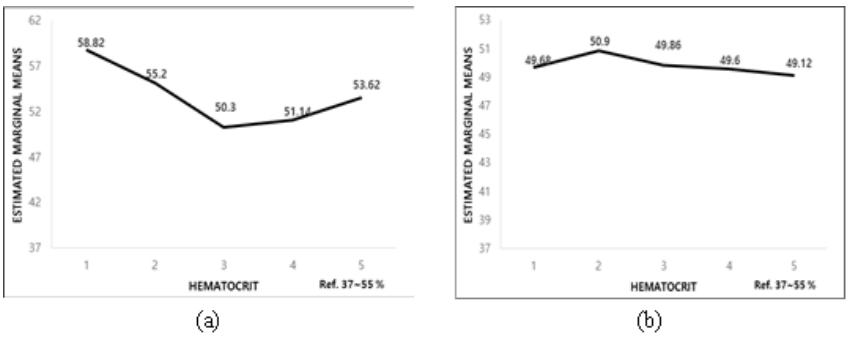
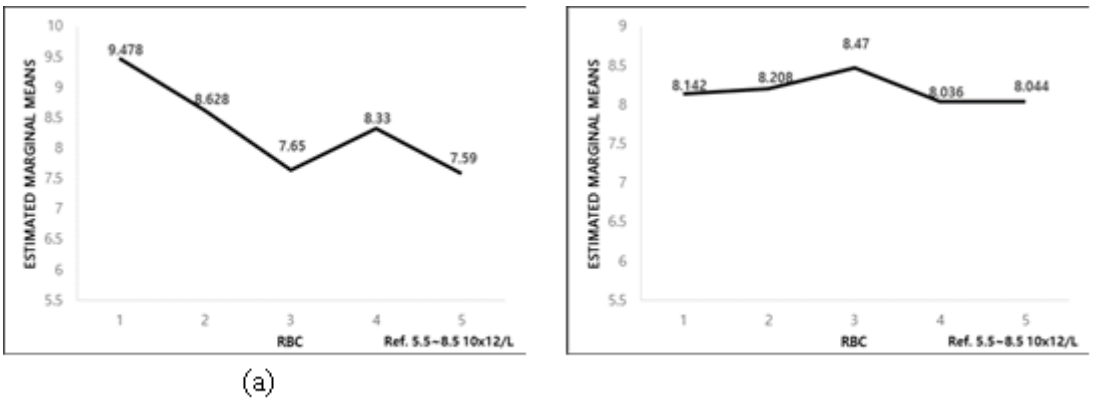


Figure 4. Mean and SD values of HCT (%) at five points for the group 1(a) and group 2(b).

Values of RBC at five points for each groups

Mean and SD values of RBC were obtained also at five points for each groups. The graphs show changes of mean RBC [106/mm3] and SD values which is illustrated in Figure 5.

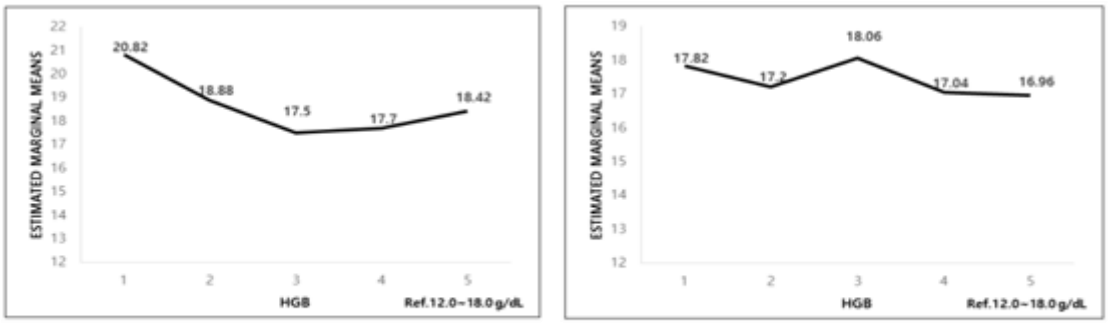


(a)

Figure 5. Mean and SD values of RBC (106/mm3) a at five points for the group 1(a) and group 2(b).

Values of HGB over five points in each group

Mean and SD values of HGB were obtained also at five points for each group. The graph of mean HGB (g/dl) and SD value is illustrated in Figure 6.

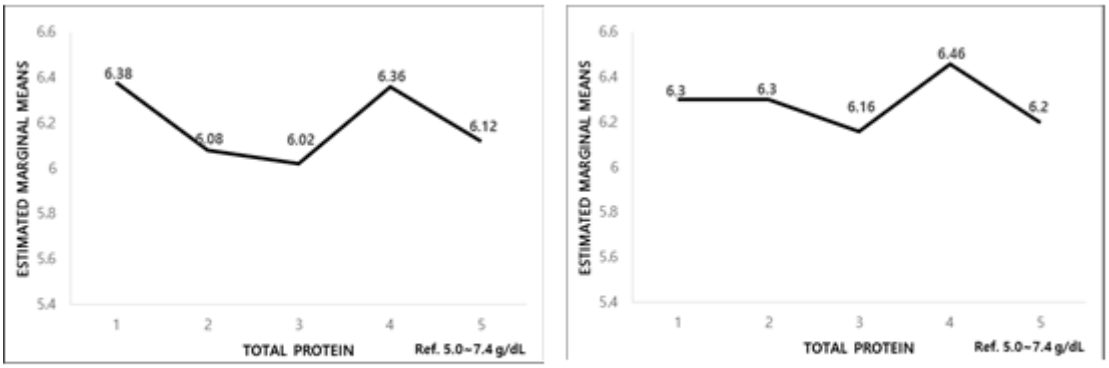


(a) (b)

Figure 6. Mean and SD values of HGB (g/dl) a at five points for the group 1(a) and group 2(b).

Values of total protein [g/dl] at five points for each groups

Mean and SD values of total protein were obtained at also five points for each two groups. The graphs of mean TP [g/dl] and SD value is illustrated in Figure 7.



(a) (b)

Figure 7. Mean and SD values of TP (g/dl) a at five points for the group 1(a) and group 2(b).

Values of globulin [g/dl] at five points for each groups

Mean and SD values of Globulin were obtained at also five points for each groups. The graph of mean Globulin [g/dl] and SD value is illustrated in Figure 8.

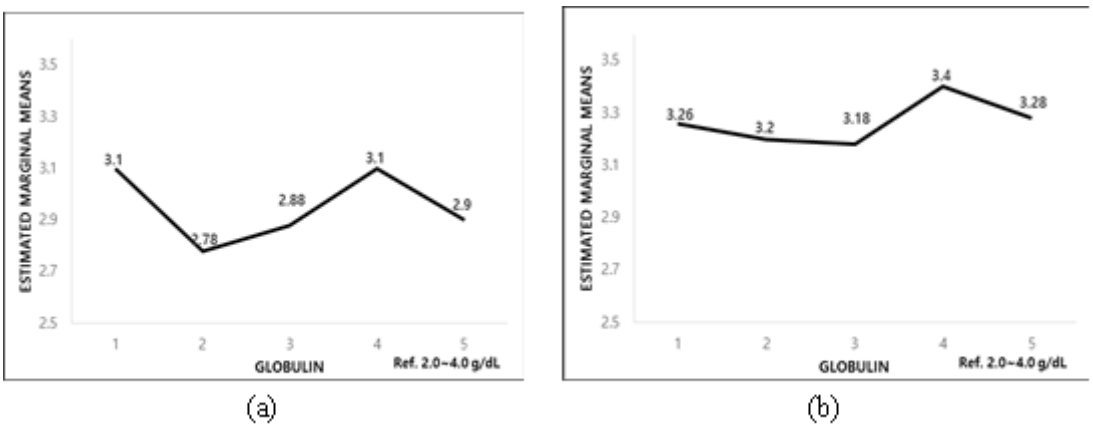


Figure 8. Mean and SD values of globulin (g/dl) a at five points for the group 1(a) and group 2(b).

Values of Fibrinogen at four points for each groups

Mean and SD values of Fibrinogen [mg/dl] were obtained at also five points. The graph of mean fibrinogen [mg/dl] and SD value is illustrated in Figure 9.

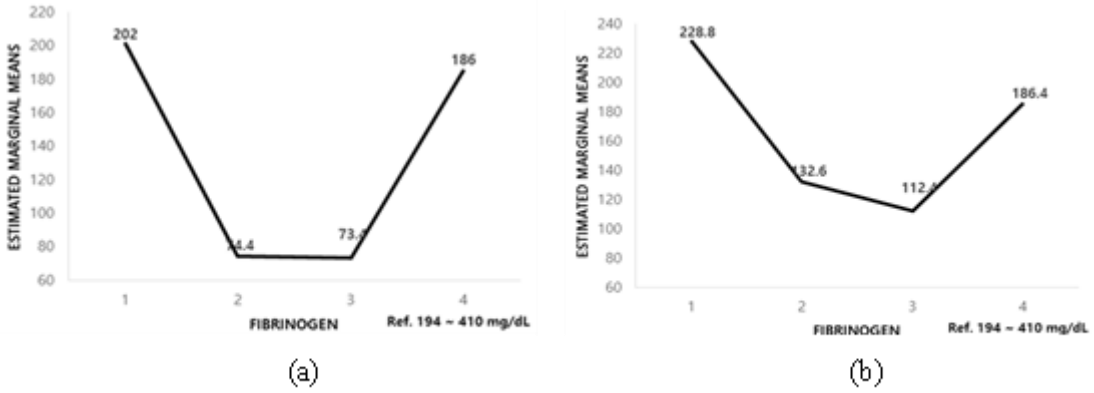


Figure 9. Changes in fibrinogen [mg/dl] mean and SD at each of four points for the group 1(a) and group 2(b).

Values of C-reactive protein[CRP] at three points

Mean and SD values of CRP were measured just before phlebotomy and immediately after phlebotomy and one day after phlebotomy. All the subjects used in the experiment were well controlled, and the values before and after phlebotomy and after one day did not change from the normal value [Ref. < 10mg/dl]. So they were not measured thereafter

Statistical significance about all factors affecting WBV at points

In this group 1 which had a high average HCT of this experiment, the changes of WBV before and after phlebotomy was statistical significant at 1 s-1 with 0.002 and 0.007 at 300 s-1. Also the changes of CBC except for HGB with p value of 0.08 were also statistical significant in the p value of 0.048 RBC and 0.046 in the p value of HCT. In serum chemistry, p value was 0.042 for globulin and 0.023 for total protein. Fibrinogen was significant[p=0.004]. In the group 2 in which HCT was within the normal reference, all of the values including WBV except the total protein with 0.02 value and the fibrinogen with 0.008 were not statistical significant.

IV. Discussion

Blood is composed of several cells including RBCs, WBCs, platelets, and plasma [aqueous solution]. Blood supplies nutrients and materials to cells in organs. It also protects the body from infection and plays an important role in maintaining homeostases such as pH, temperature, and blood pressure [22, 23]. Although there

are some common methods for examining the blood such as CBC, chemistry, and blood gas analys is, they can not be used in the diagnosis of diseases that occur when WBV, which is related to blood vessels and velocity, is abnormal.

We know that WBV values depend on HCT, plasma proteins, and the agglutination and deformability of red blood cells [4, 6–8]. Of these determinants, HCT has the greatest influence on WBV. HCT, which is also used interchangeably with PCV, is the volume percentage [%] of RBCs in the blood [4, 24]. Secondary factors that may have an additional effect on WBV include inflammatory disorders and sex hormones. In a human study, males had higher values of HCT and fibrinogen than females because of blood loosing during menstruation and the viscosity was also high. In this experiment, all the individuals were neutered to reduce the effect of sex hormones [25–27]. CRP, which is another secondary factor, is a common cause of increased red blood cell aggregation. In humans, CRP is produced from an inflammatory reaction after tissue damage caused by injury, infection, and various disorders [28]. In this experiment, immediately before and after the phlebotomy and 24 hours after, mean CRP values of all dogs were under the reference range [10–20 mg/dl]. Consequently, we were able to exclude secondary effects such as inflammatory disorders and sex hormones on WBV.

Polycythemia refers to the abnormal elevation of PCV, red blood cell [RBC] count, and hemoglobin concentration. Especially in dogs, PCV is more than 80 %, but clinicals ymptoms are secondary when WBV exceeds 60 %. Polycythemia can be divided into relative, which can be thought of as dehydration, and absolute, which is based on RBC mass; the absolute can be classified as primary and secondary depending on the causes. Several diagnostic methods can be used to differentiate them, and the treatment method will vary depending on the results. Relative polycythemia can be treated with fluid therapy, and absolute can be treated with phlebotomy [18, 29, 30]. Changes in WBV associated with the clinical symptoms of polycythemia are due to endothelial dysfunction in which vasoactive factors are not released, resulting in a change in HCT and fibrinogen values. Diseases that may result from these outcomes include cardiocerebrovascular disease, diabetes mellitus, hemorrhagic shock, and secondary diseases like renal failure. For these diseases, if the HCT is in the normal range with high viscosity, it can be treated through plasma exchange, and if the HCT and WBV are abnormally high, it should be treated through phlebotomy or fluid therapy or a combination of those methods [14]. Roos found that if the WBV is high when the HCT is normal, there are no such problems [31]. However, Benisand Murray observed that if the HCT and the WBV are simultaneously high [32], various diseases may occur. Thus, WBV measurements should be taken routinely if the HCT is abnormally high. Among the aforementioned methods, experiments were carried out on 10 healthy subjects in order to examine how the WBV values and related patterns change due to phlebotomy. Generally, the volume of blood in phlebotomy for an 11.7 kg polycythemia patient should be 172.5 ml, according to the 10% rule, and the HCT should be obtained after the phlebotomy. However, considering that the subjects were healthy and that in one study of 4 weeks of serial phlebotomies in beagles, one fourth of this value was taken [30], we obtained 40 ml of blood [5 ml for each blood tests before and after the phlebotomy and 30 ml for the phlebotomy].

Considering that the mean and standard deviation of the HCT value was 44.7 ± 4.2 in one study [20], the first group in this study consisted of individuals with HCT values of 50 or above, and the second group consisted of individuals with HCT values within the reference range. The mean values for each group were 58.82 and 49.68. The WBV values for the first and second groups at SR 1 s-1 were 39.744 and 37.242 and those at SR 300 s-1 were 5.754 and 5.106, respectively. The correlation between HCT and WBV in these two groups was determined by linear regression analysis. The r2 values were 0.6168 for SR 1 s-1 and 0.5615 for SR 300 s-1, indicating that the relationship between HCT and WBV was significant. These values were almost the same as the values of 0.6286 for SR 1 s-1 and 0.6121 for SR 300 s-1 obtained in a previous study when determining the reference range of WBV in 82healthy beagles [33]. The changes in WBV and its associated values before and after the phlebotomy in the two groups with this significance were examined. The results of this experiment showed that the phlebotomy significantly affected all the values, except for HGB, in group1, whereas in group2, most of the values including viscosity were not significantly affected by the phlebotomy. This means that the phlebotomy did not have a significant effect on theindividuals with normal values of HCT but had a substantial effect on individuals with high HCT and WBV values.

In group 1, changes in viscosity and associated values before and after the phlebotomy showed a compensatory response after large volumes of blood loss. The immediate response is splenic contraction, and erythropoiesis occurs in bone marrow over a long period of time [34]. It was confirmed that splenic contraction occurred by examining the changes after 24hours, which were larger than those immediately after the change of HCT, and th erelatively immediate change of fibrinogen and total protein was larger than that after 24hours. The change in the total serum protein [TSP] immediately after the phlebotomy was larger because the volume expansion from hypovolemia progressively diluted both PCV and TSP. The aforementioned splenic response in itially boosted red cell numbers. Therefore, TSP tended to drop rapidly within 1 to 4 hours and the PCV values subsequently decreased after around 24 hours [35]. The changes in WBV also had similar results as the changes in HCT. We, thus, confirmed the close relationship between viscosity and HCT.

In the blood cell cycle, stem cells that can differentiate into platelets, erythrocytes, and lymphocytes become reticulocytes after 7 days of progenitor and precursor cell processes and extruding of the nucleus. These reticulocytes migrate into the blood vessel after 1 to 2 days and become fully mature cells [36, 37]. The HCT level recovered only after 7 days of the phlebotomy. However, the p value for the change between 1 day and 7 days after the phlebotomy was greater than 0.05, which means that it was not significant. The recovery of the HCT was due to a compensatory reaction for 2 to 3 weeks after large blood loss [35], and it is thought that the collection of the blood was done when the reticulocytes migrated to the blood vessel . Unlike this slight change in HCT, WBV recovered to a similar level as before the phlebotomy, and the value of fibrinogen was similar to the previous value. Therefore, we believe that fibrinogen, one kind of plasma protein, plays an important role in viscosity recovery after 7 days of phlebotomy.

Limitation of this study consists secondary factors including sex hormones and inflammatory disorders were excluded. However, the elevation of WBV as a result of the stress of being restrained was not prevented. Selecting a more tractable object or giving the beagles enough time to adapt to the handler would potentially solve this issue [38]. To observe the life cycle of the red blood cells properly, the blood test should have been performed around 7 days, and the smear evaluation should have been done, but this evaluation was not performed.

V. Conclusion

In this study, we were able to identify which blood test values affected the change of viscosity before and after the phlebotomy. And in the group with elevation of HCT, it is confirmed that the changes of viscosity and general blood test were significant when the phlebotomy is performed as one method for solving various diseases that may occur when HCT and WBV value were simultaneously high.

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