Spleen Factor: The Spleen's Role as a Respiratory Organ

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ABSTRACT

The Bajaus' ability to free dive for prolonged periods is attributed to their exceptional physiologic response and large spleens. The spleen has been traditionally viewed as a hematologic and immunologic organ. Unconventionally, this review explores the spleen's role as a respiratory organ and how apnea training can enhance the spleen's form and function. Eligible articles obtained from *Pubmed* were discussed. The selected studies have shown that an 8-week home-based apnea training regimen can enhance the spleen volume by as much as 24% and that prolonged apnea training can increase both splenic contraction and baseline serum hemoglobin levels. However, the sample size and heterogeneity of these studies largely limit the generalizability of these findings. Thus, several future studies are needed to further explore the spleen's respiratory function in humans.

Keywords: Spleen, divers, apnea training

INTRODUCTION

The Bajau people are a group of sea nomads in Southeast Asia that have been living an entirely marine-dependent life for over 1,000 years.[1] They spend 60% of their time underwater to gather food in depths up to 70m with nothing more but a set of weights to keep them submerged and a pair of wooden goggles to provide clear vision.[2,3] The Bajau's superhuman ability of freediving for prolonged periods is attributed to their exceptional physiologic diving response. This response is composed of bradycardia, peripheral vasoconstriction, and splenic contraction to reduce oxygen consumption, protect hypoxia-sensitive organs, and increase oxygenated red blood cell (RBC) levels, respectively.[4-6] More recently, the Bajaus were also found to have genetically adapted larger spleens which allow them to actively hunt for food underwater in spite of prolonged apnea.[7] This exceptional respiratory ability to tolerate hypoxia is attributed to their larger spleens. Viewing the spleen as a respiratory organ is a relatively uncommon perspective given that it is traditionally viewed as a hematologic and immunologic organ. This paper reviews literature on the spleen's role as a respiratory organ and how apnea training can enhance the spleen's form and function.

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METHODS

This article reviews the spleen's respiratory function in humans. Articles were extracted from *PubMed* using the query ((Spleen [MeSH Terms]) AND (Apnea [MeSH Terms])) AND (Training). Publications from January 1, 2000 to December 31, 2019 investigating the effects of apnea training on baseline spleen volume, splenic contraction, and total hemoglobin were included. Studies not directly measuring these parameters were excluded as illustrated in *Figure 1*. Articles were independently screened by the authors and consensus was made for each included article to avoid selection bias. Data on baseline spleen volume, splenic contraction, and serum hemoglobin about apnea training were extracted from the selected works and utilized in the current review. Studies on the Bajau and the spleen's normal response to hypoxia were supplemented to provide an introduction and supporting information for discussion.

RESULTS

The five selected studies were by Bouten et al., Engan et al., Bakovic et al., Richardson et al., and Prommer et al. [11,14,16,17,24] The first two studies investigated the effects of home-based apnea training on spleen and hemoglobin parameters, the third study compared splenic contraction between apnea-trained divers and untrained persons, while the last two studies observed the effects of long-term apnea training via diving on spleen size and hemoglobin levels. Among the studies, there is a clear difference in sample size and demographics (i.e., Bouten et al., recruited 13 healthy

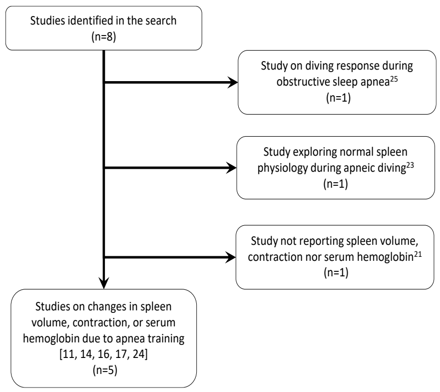

Figure 1. Study selection process

males while Richardson et al., recruited 78 divers, skiers, and untrained individuals from both sexes) (see *Table 1*). Bakovic et al. did not explicitly state their inclusion and exclusion criteria while the criteria were similar in the other four studies. They were all at least 18 years old with smoking and alcohol intake prohibited. The measured parameters were also similar among the studies but the measurement tools used in each study varied (i.e., venous blood extraction vs. intravenous catheter vs. CO-rebreathing method for hemoglobin concentration). Due to the apparent heterogeneity of the selected studies' design, sample size, demographics, and measurement tools, this paper's discussion will be limited to reviewing the selected articles' results and findings as separate works.

DISCUSSION

Normal Response to Hypoxia. When we hold our breaths for a long time, our bodies enter a state of hypoxia. As a response to compensate, our bodies have evolved short and long-term adaptations. The first short-term adaptation is the cardiovascular response. This involves peripheral vasoconstriction and bradycardia.[8,9] This is to reduce the body's oxygen uptake during apneic events. Interestingly, face-immersion in cold water during diving also acts as a stimulus for this response.[3] The next short-term response, which will be the focus of this paper, is splenic contraction. As oxygen intake is decreased during apnea or breath-holding, the spleen contracts releasing stored RBCs into circulation to increase blood oxygen storage and transport capacity.[10,23] The spleen acts as an RBC reservoir that is tapped during apneic events to ameliorate oxygen deficiency. Moreover, when apnea events occur more frequently and are more prolonged, the body will develop a long-term adaptation. This strategy refers to increased serum erythropoietin (EPO) concentration after repeated apnea events.[11,12] Erythropoietin is a hormone produced mainly in our kidneys that stimulate RBC production which will then increase blood oxygen storage capacity. All these occur in unison with other well-known responses to apnea such as serum acid-base balance to avoid hypoxia-related injuries.

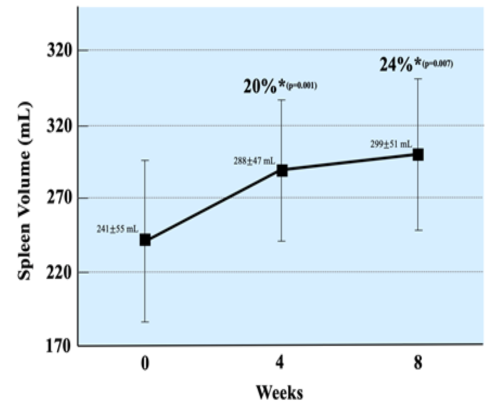

Figure 2. Baseline spleen volume increased by 20% after 4 weeks of the program, then 24% after 8 weeks of the program (n=13, P=0.05). (Bouten et al., 2019).

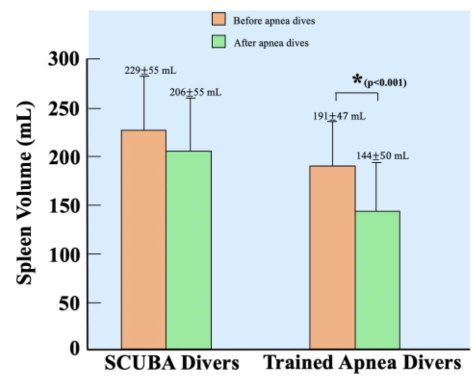

Figure 3. Trained apnea divers showed a significant difference between pre-and post- apnea dive spleen volume. (n=17, P<0.05)[16]

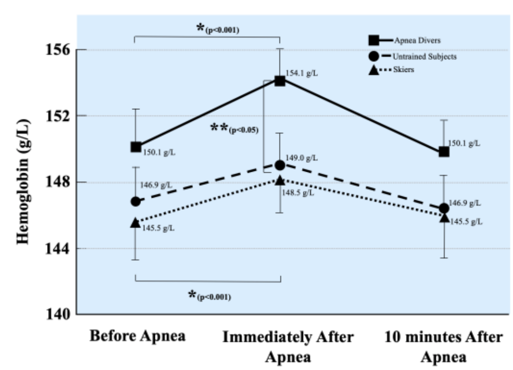

Figure 4. All groups showed significant difference between baseline and post-apnea hemoglobin levels *(p<0.001). Additionally, apnea divers showed a greater increase in serum hemoglobin when compared to skiers and untrained subjects (pooled) **(p<0.05). Baseline hemoglobin was also noted to be increased in apnea divers in comparison with the control groups (skiers and untrained subjects)[14]

Table 1. Characteristics and Summary of Included Studies

Parameter	Bouten et al., (2019)	Engan et al., (2011)	Bakovic et al., (2003)	Richardson et al., (2005)	Prommer et al., (2007)
Type of Study	Experimental	Experimental	Observational	Observational	Observational
Sample size	n=13	n=10	n=27	n=78	n=36
Drop-outs	0	0	0	0	0
Demographics	n=13 M	n=6 M n=4 F	Trained Apnea Divers n=10 Untrained n=10 Splenectomized n=7	Divers n=29 M n=4 F Skiers n=13 M Untrained n=23 M n=9 F	Apnea Divers n=7 M n=3 F SCUBA Diver Controls n=7 M Non-Diver n=10 Untrained n=9 Triathlete
Age	22±1.4 years	25±6 years	Trained Apnea Divers 28.6 ± 1.7 Untrained 27.8±3 Splenectomized 23.7±1.1	Divers 30.3±10.6 years Skiers 20.2±3 years Untrained 30.0±6.3 years	Apnea Divers 35±9 M 32±6 F SCUBA Diver Controls 38±11 Non-Diver 31±10 Untrained 31±8 Triathlete
Height	1.79±0.05 m	175±11 cm	Trained Apnea Divers 185.6±2.4 Untrained 185.7±1.4 Splenectomized 183.0±1.4	Divers 181.5±8.5 years Skiers 180.6±6.2 cm Untrained 177.6±8.0 cm	Apnea Divers 184±6 M 174±9 F SCUBA Diver Controls 180±6 Non-Diver 179±4 Untrained 186±7 Triathlete
Inclusion criteria	18 to 30-year-old males with good general health and exercises 2 times a week on average.	19 to 31-year-old healthy and moderately fit individuals.	Not stated	At least 18 years old.	Divers with regular apnea training for 2-3 hrs of training 3 times per week for at least 3 years. SCUBA divers without long-term apnea training
Exclusion criteria	Smoking, experience with breath-holding sports, residing at high altitudes and blood donation within 3 months from start of the study.	Smoking and regular participation in breath-holding sports.	Not stated	Divers who lived in high altitude 6 months prior. Skiers with experience in breath-holding, recently joined a competition and lived in high altitude 6 months prior. Untrained individuals with experience in breath-holding, athletic training, and lived in altitude 6 months prior.	Smoking, alcohol and caffeine intake were prohibited before the study.
Parameters measured	Apnea duration, serum hemoglobin, and spleen size.	Apnea duration, mean arterial pressure, breathing movements, serum reticulocytes, serum hemoglobin, spleen size, heart rate, and O_2 saturation.	Apnea duration, spleen size, splenic blood flow, spleen vessel diameter, arterial blood pressure, oxygen saturation, heart rate, transcutaneous oxygen and carbon dioxide partial pressures	Apnea duration and serum hemoglobin.	Total hemoglobin mass, spleen size
Measuring tools	Timer, venous blood extraction, ultrasound system	Multichannel data acquisition system (BioPac), venous blood extraction, ultrasound system, pulse oximeter, and photoplethysmometer	Ultrasound system, ECG, pulse oximeter, heart rate monitor, spirometer	Timer, intravenous catheter and capillary blood analysis	CO-rebreathing method, arterialized blood samples, and ultrasound system
Intervention	Eight weeks of home-based apnea training where subjects performed five breath-holds while seated every day.	Two weeks of home-based training where subjects performed 10 maximal apneas divided into 2 sets with 10 minutes rest in between sets.			
Assessment	Apnea duration, hemoglobin concentration, and spleen size were measured before commencement of the training program, after 4 weeks of training and after 8 weeks of training.	Apnea duration, mean arterial pressure, breathing movements, serum reticulocytes, serum hemoglobin, spleen size, heart rate, and O_2 saturation were measured during each apnea test which was conducted before and after 2 weeks of training.	Apnea duration, splenic blood flow, splenic vessel diameter, spleen size, diving response, and transcutaneous blood glasses were measured before, during, and after a series of five maximal apneas.	Hemoglobin levels were measured before apnea, immediately after apnea and 10 minutes after apnea.	Spleen volume and hemoglobin levels were measured before and after five apnea dives.

Spleen's Response to Apnea. The spleen contracts in response to oxygen deficiency. This contraction is via α-2 adrenergic stimulation of adrenergic receptors found in the spleen's capsule and parenchyma which activates contractile proteins to decrease the spleen volume.[13] As the spleen decreases in volume, it squeezes out stored RBCs which translate into increased serum hemoglobin concentration for increased oxygen delivery.[10] To further increase oxygen reserves during apnea, a spleen with a larger baseline volume will be advantageous – as seen in Bajaus. Therefore, a superior spleen is bigger and has a greater magnitude of contraction to further increase serum hemoglobin concentration. It is then logical to ask if the spleen can be enhanced by any means to increase oxygen reserve that may be of utility in aerobic activities such as running and exercise. This question will be answered in the following sections.

Enhancing Baseline Spleen Volume. Bouten et al. aimed to investigate the effects of an 8-week home-based apnea training program on baseline spleen volume, contraction, and hemoglobin levels in healthy male participants. Spleen size was measured via ultrasound while hemoglobin concentration was measured using an automated hematology analyzer. Engan et al., aimed to measure similar outcomes but instead of 8 weeks, a 2-week home-based apnea training program was the intervention. Details on inclusion and exclusion criteria as well as subject characteristics are summarized in *Table 1*. The 8-week training regimen involved doing five seated breath holds (2 minutes of rest in between) every day, while the 2-week regimen involved doing ten breath holds every day in the same manner. Bouten et al., measured spleen size and hemoglobin concentration on weeks 0, 4, and 8, and employed repeated measures ANOVA to analyze between and within parameter differences during the three testing sessions, while Engan et al., reported the same parameters (except baseline spleen volume) on weeks 0 and 2 and employed a paired t-test to compare parameters before and after training. Significance was set to $p<0.05$ for both studies. Bouten et al., found that baseline spleen volume was 20% larger after four weeks (241±55 mL to 288±47 mL; p=0.001) and 24% larger after eight weeks (241±55 mL to 299±51 mL; p=0.007) of training (see *Figure 2*). Baseline hemoglobin concentration was also observed to increase by 3.3% after four weeks of training (153 ± 10 g/L to 158 ± 9 g/L; p = 0.004) and remained at this level through the 8th week of training. However, splenic contraction did not show significant difference between testing days. Similarly, Engan et al., did not find significant changes in both splenic contraction and hemoglobin concentration after 2 weeks of training which will be discussed in the next section.

Findings of Bouten et al., then implies that more frequent and longer apneas produce larger spleens. The exact mechanism of how apnea stimulates splenic growth remains obscure. But it is likely that chronic hypoxia stimulates EPO production to increase total RBC count and this increase in RBCs then require an enlargement of its reservoir, the spleen.[13]

On the other hand, some individuals are genetically predisposed to be born with a larger spleen. The Bajau people were recently discovered to have a notable genetic variant in the PDE10A gene—a gene shown to be associated with spleen size and thyroid function.[13] PDE10A is a cyclic nucleotide phosphodiesterase involved in smooth muscle contraction including those that surround the spleen thus possibly influencing splenic size and contraction.[7] Additionally, the single nucleotide polymorphism of the PDE10A gene favored in the Bajaus renders them "resistant" or less likely to develop hypothyroidism. Relating thyroid function and spleen size were explored in an animal study, where increased levels of thyroid hormones were observed to increase spleen size in mice with a small spleen phenotype. Similarly, in humans, thyroid hormones are known to regulate normal erythropoiesis during early postnatal development, thus the large spleen phenotype observed in Bajaus may be a result of increased erythrocyte volume.[13]

Enhancing Splenic Contraction. Aside from an increased baseline spleen volume, a spleen with a great degree of contraction will provide a significant oxygen boost during apneic events. The study by Prommer et al. aimed to determine the effect of repeated apneas on spleen size and total hemoglobin mass of trained apnea divers (regular apnea training ≥3 years) as compared to SCUBA divers in both non-diving endurance-trained and untrained individuals. Spleen size was measured via ultrasound and total hemoglobin mass was assessed via the CO-rebreathing method.[16] Details on inclusion and exclusion criteria as well as subject characteristics are summarized in *Table 1*. Spleen size was measured before and immediately after five repeated apnea dives. Total hemoglobin mass was obtained 9 mins after the last dive. A paired t-test was used to compare before and after spleen volumes within a group while one-way ANOVA with posthoc *Scheffe test* was used to compare hemoglobin measures between groups. Significance was set to $p<0.05$. Before the dive, spleen volume was not significantly different ($p=0.142$) between the trained divers (229±55 mL) and the controls (191±47 mL) but after the dive, the control group had a significantly ($p=0.029$) larger spleen size (206±55 mL) when compared to the trained divers (144±50 mL) due to the significantly larger degree of splenic contraction found in the trained apnea divers ($p<0.001$) (see *Figure 3*).[16]

Similarly, Bakovic et al. also compared splenic contraction between trained apnea divers and untrained individuals. Spleen size was measured before, during, and after apneic periods. Friedman's ANOVA was used to compare before and after apnea measures, and Wilcoxon's signed-rank test was applied when a significant difference was found. Significance was set to $p<0.05$. Although mean values were not reported, the study found that apnea divers had a significantly greater degree of contraction when compared to untrained individuals ($p<0.001$).[24] A limitation of this study is the non-reporting of inclusion criteria which may have helped in evaluating the chronicity of the trained diver's experience.

Furthermore, these findings are in contrast to the findings of Bouten et al., and Engan et al., that 2 to 8 weeks of apnea training is insufficient to create a significant effect on splenic contraction. This then suggests that years of apnea training is necessary to enhance spleen contraction; findings which are similar to those seen in the works of Prommer et al., and Bakovic et al.[17] In addition, Prommer et al., reports that there was no significant difference in total hemoglobin mass values among the groups implying that the trained divers did not have a significant advantage of having increased total hemoglobin. This was rationalized by stating that the diver's hypoxic duration was probably not long enough to stimulate effective erythropoiesis.[16] This observation on hemoglobin values contradicts the findings of Richardson et al.

Enhancing Hemoglobin Concentration. An increased RBC reservoir and a more powerful splenic contraction will allow more RBCs to be released into the systemic circulation, thus an increased splenic volume and contraction should secondarily increase hemoglobin concentration. Richardson et al. aimed to compare the hemoglobin concentration of trained apnea divers (5.5±4 hrs of apnea training per week) versus skiers and untrained divers after periods of apnea. Serum was obtained via an intravenous catheter and capillary blood sampling and was analyzed via automated blood analysis units and hemoglobin analyzers. Details on inclusion and exclusion criteria as well as subject characteristics are summarized in *Table 1*. Blood samples were obtained 2 minutes before three repeated apneas (with 2 mins rest in between), immediately after the last apnea, and 10 minutes afterwards. Hemoglobin values were compared within groups via paired t-test and comparison between groups was made via unpaired t-test. Significance was set to $p < 0.05$. Apnea divers had the highest baseline hemoglobin concentrations among the groups (apnea divers: 150.1 g/L; untrained subjects: 146.9 g/L; skiers: 145.5 g/L). After the apneic episode, all groups showed increased hemoglobin concentrations but the apnea divers showed a significantly higher increase in hemoglobin concentrations when compared to the other two groups ($p < 0.05$). However, 10 minutes post-apnea, hemoglobin levels were observed to return to baseline (see *Figure 3*). This may explain the contradicting findings of Prommer et al., where total hemoglobin levels were observed around 9 minutes after apnea. This and the different methodology in measuring hemoglobin may account for the contradicting findings of these two studies. Additionally, Engan et al.'s report of no significant difference in hemoglobin concentration between pre- and post-2-weeks of training may be due to the relatively short training period of their study.

Applicability in Athletic Events. Aerobic performance is largely influenced by the body's capacity to deliver oxygen to active musculature.[19] Given that the overall effect of enhancing the spleen is increasing the amount of stored oxygenated RBCs that will be available during aerobic events, spleen enhancement may have significant contributions in the future of improving athleticism.[20] Other than enhancing spleen volume, contraction, and hemoglobin levels, another important benefit from apnea training is increasing EPO levels.[11,12,16,21] The use of recombinant human erythropoietin and its analogs are banned by the world anti-doping agency and other sports authorities for obvious reasons --- they serve as artificial drugs for enhancing aerobic performance.[22] Therefore, a finding that repeated apneas can naturally increase EPO production by 24% highlights the potential of apnea training in enhancing tissue oxygenation. Moreover, apnea training has also been shown to increase lung volumes and provide an apparent resistance to blood acidosis and oxidative stress.[20] Since training the spleen can only be done via apnea training, to do so would provide an athlete these advantages. Going back to the Bajaus, it is then worth considering that this group of sea nomads may harness the untapped athletic potential that goes well beyond diving for food.

CONCLUSION

There is a scarcity of recent works investigating the effects of apnea training on the spleen's form and function. Nevertheless, the selected works have shown that the spleen acts as an RBC reservoir that increases oxygenation during apnea, and that it can be enhanced to be larger and store more RBCs. It was also reported that years of training can enhance splenic contraction to release more RBCs during apnea and increase serum hemoglobin concentration. Taking all these into account, it is clear that enhancing the spleen via apnea training has the potential to improve athletic performance in aerobic events. However, the small sample size and heterogeneity of these studies largely limit the generalizability of these findings. Therefore, several future studies are needed to further investigate this understudied role of the spleen as a respiratory organ.

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