Physical and cognitive performance after blood donation

A clinical study to investigate donor safety in walking blood banks

Håkon Skogrand Eliassen

Thesis for the degree of Philosophiae Doctor (PhD)
University of Bergen, Norway
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List of abbreviations and terms

Abbreviations

ATP – Adenosine triphosphate

$_{ABS}VO_{2MAX}$ - Absolute maximal oxygen consumption

[Hb] - Hemoglobin concentration in blood

HR – Heart Rate

HVTL – Hopkins Verbal Learning Test

HVTL-R – Hopkins Verbal Learning Test-Revised

MJK - Marinejegerkommandoen (Norwegian name of NORNAVSOC)

NORNAVSOC - Norwegian Naval Special Operations Commando

RAAS – Renin – angiotensin – aldosterone system

$_{REL}VO_{2MAX}$ - Relative maximal oxygen consumption

THOR – Trauma, Hemostasis, and Oxygenation Research Network

TMT-A – Trail Making Test A

TMT-B – Trail Making Test B

VO_{2MAX} – Maximal oxygen consumption

WWI – World War I

WWII – World War II

Terms

FAR FORWARD – Situations where medical resources are scarce and evacuation to definite care is severely prolonged.

MEDIC – A soldier trained in and responsible for medical care on missions.

SHOT – Serious Hazards Of Transfusion, The UK hemovigilance scheme

SMO – Senior medical officer in a military unit responsible for advising the unit's command on health-related issues.

TROLL – Overvåkning av blod i Norge, The Norwegian hemovigilance system

WALKING BLOOD BANK – Volunteer blood donors screened and selected as regular donors who only donate blood when needed.

WALKING DONOR – A blood donor in a walking blood bank.

WHOLE BLOOD – Unfractionated anticoagulated donor blood.

Scientific environment

The Norwegian Naval Special Operations Command (NORNAVSOC) is one of two special operations commands in Norway. A special operations command differs from conventional forces in several aspects. The personnel are selected, the equipment is specialized, and the tactics are advanced. Most importantly, the missions are unique. These forces operate behind enemy lines, far from allies and support. Personnel enduring this life and solving these missions are a different breed. They have intense stamina and are innovative and adaptable. However, they are also human and at high risk of injury. In 2009 the idea of revitalizing buddy transfusion far forward to save injured personnel in hemorrhagic shock arose in this environment.

Blood Far Forward research group was initiated by the Norwegian Naval Special Operation Commando and the Department of Immunology and Transfusion Medicine at Haukeland University Hospital in 2010. Today the group's collaborators include the Norwegian Armed Forces Medical Services, the United States Army Institute of Surgical Research (USA), and the National Health System Blood and Organ transplant (UK).

The initiative to host an international conference on transfusion-related topics in 2011 led to the establishment of an international multi-disciplinary research network: Trauma, Hemostasis, and Oxygenation Research Network (THOR). In 2022 the 10th annual conference was arranged by this non-profit organization, and it gathered approximately 170 participants from more than 20 different nations in Os, outside Bergen. The group strives to gather the whole span of medical providers, from medics on the battlefield to professors of medicine.

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Professor Einar Thorsen, at the Department of Work Physiology at Haukeland University Hospital, helped develop a protocol for VO_{2MAX} testing on an ergometer bike in Paper III.

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Finn Eliassen, my dear father, you are always with me, which is why this project has been finalized. You taught me never to give up.

Abstract

Whole blood transfusion for patients in hemorrhagic shock has been re-introduced over the last two decades. In walking blood banks, the blood is stored in the original container until needed. The concept is logistically feasible, cost-effective, and provides access to whole blood where blood bank services are unavailable. Walking blood banks are important in Norwegian health care`s blood preparedness plans.

The Norwegian Naval Special Operations Command identified walking blood banks as the only option to ensure whole blood availability in far-forward missions. However, a major concern was that blood donation would compromise the soldiers' skills, and the literature did not provide convincing evidence to implement the system.

Therefore, a study was designed to investigate feasibility; would blood donation affect elite soldiers' endurance and shooting capabilities – and would it be possible to train non-medics in blood donation procedures? As shown in Paper I, we did not find reduced maximal oxygen consumption or impaired soldier skills in rested soldiers. There was a 100% success rate in teaching non-medics in whole blood donation and transfusion procedures. The Naval Special Operations Command approved walking blood banks based on these findings. However, as the study was conducted on rested soldiers, the results could not be transposed to soldiers in combat situations. The next study accordingly was designed to investigate the physical performance of fatigued soldiers immediately after blood donation. Paper II showed a 6% reduction in maximal oxygen consumption in fatigued soldiers, which was considered acceptable by the Command.

In Norway, with long transportation distances and challenging weather conditions, a walking blood bank is considered a real possibility, also in civilian settings. It was consequently logical to include regular blood donors in the third paper: Would their physical and cognitive functions significantly reduce after blood donation? In Paper III, we report a 7% reduction in maximal oxygen consumption and that cognitive performances were maintained in regular blood donors. A standard blood donation causes a decrease in exercise physiology, does not affect cognitive physiology, and maintains performance. Therefore, walking blood banks are feasible and provide resilience. However, some of the risks involved should be acknowledged. Future quality data is warranted to reduce residual risk, especially in different environmental settings.

Sammendrag

De siste 20 årene har fullblod til pasienter i blødningssjokk blitt re-lansert som foretrukket behandling. I vandrende blodbanker blir blodet oppbevart i original forpakningen inntil behovet oppstår. Konseptet har logistiske fordeler, er kost effektivt og bevarer tilgang til fullblod både når man er på oppdrag langt fra andre ressurser eller ved kriser. Vandrende blodbanker utgjør i dag grunlaget for nasjonale planer for blodberedskap i Norge.

Marinejegerkommandoen etablerte vandrende blodbanker blant deres soldater for å sikre tilgang til fullblod på oppdrag med lange evakuerings akser. I den forbindelse ble det reist spørsmål om mulig reduksjon i yteevnene og soldatferdigheter like etter blodgivning. Litteratursøk gav ikke tilfredsstillende svar på spørsmålene.

Derfor ble det designet en studie for å utforske hvordan blodgivning påvirket spesialsoldatenes utholdenhet og ferdigheter, samt om det var mulig å lære ikke-sanitetspersonell tappe prosedyrer. I Artikkel I fant vi hverken redusert maksimalt oksygenopptak eller reduserte ferdigheter hos uthvilte soldater. Det var og 100% suksessrate for opplæring i tappeprosedyrer. Dette førte til at Marinejegerkommandoen etablerte vandrende blodbanker blant sine soldater. Funnene var gjort hos uthvilte soldater og kunne trolig ikke overføres til slitne soldater på slagmarken. Neste studie undersøkte derfor effekten av standard blodgivning hos utslitte soldater. Artikkel II viste ett fall i maksimalt oksygen opptak på 6%, noe som var akseptabelt for Marinejegerkommandoen.

I Norge kan avstander mellom sykehus være lange og været ofte utfordrende. Derfor er vandrende blodbanker brukt også sivilt. Dette gjorde det naturlig å designe en studie som undersøkte effekten av blodgivning på fysisk og kognitiv yteevne hos vanlige blodgivere, og i Artikkel III fant vi 7% reduksjon i maksimalt oksygenopptak og bevart kognitiv yteevne.

Vandrende blodbanker er et trygt og effektivt system for å sikre tilgang til fullblod ved kriser eller ved lange evakuerings og forsynings akser. Å gi blod påvirker blodgiverens yteevne i begrenset grad, men å gi blod i en krisesituasjon kan sette blodgiveren i fare om han eller hun skulle bli den neste pasienten. Fremtidige studier er ønsket for å sikre funnen samt å undersøke effekten av blodgivning under andre miljømessige forhold.

List of Publications

Paper I

Donor performance of combat readiness skills of special forces soldiers are maintained immediately after whole blood donation: a study to support the development of a prehospital fresh whole blood transfusion program

G. Strandenes, H. Skogrand*, P. C. Spinella, T. Hervig and E. B. Rein

Transfusion 2013 Vol. 53 Issue 3 Pages 526-30,

*Author changed the last name to Skogrand Eliassen in 2015.

Paper II

Making whole blood available in austere medical environments: donor performance and safety

H. S. Eliassen, A. Aandstad, C. Bjerkvig, T. Fosse, T. A. Hervig, H. F. Pidcoke, et al.

Transfusion 2016 Vol. 56 Suppl 2 Pages S166-72

Paper III

Immediate effects of blood donation on physical and cognitive performance a randomized controlled double-blinded trial

H. S. Eliassen, T. Hervig, S. Backlund, J. Sivertsen, V. V. Iversen, M. Kristoffersen, et al.

J Trauma Acute Care Surg 2018 Vol. 84 Issue 6S Suppl 1 Pages S125-S131

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Introduction

1.1 The origin

NORNAVSOC was deployed on a frigate to the Gulf of Aden on a counter-piracy mission in 2009. The author of this thesis was then one of the soldiers and the medic in the Special Operations Forces (SOF) team. Medical resources on board included a surgical team. Historically, blood and blood products had been used in pre-hospital situations (1, 2, 3, 4), but had become controversial at the time (5). Despite this, the frigate crew had volunteered to participate in a walking blood bank, representing the blood supply for the surgical team.

Operating at sea is challenging. Weather changes rapidly and severely affect the speed of travel for fast boats the er used for operations. On missions, evacuation time to the frigate could be 24-72 hours or more. Current treatment protocols for hemorrhagic patients pre-hospital at the time recommended a rapid infusion of balanced salt solution, which I carried as the team medic. Data on the possible advantages of blood and blood products over balanced salt solutions for hemorrhagic trauma patients with delayed evacuation were emerging (6, 7, 8), and in contrast with my plan for treating my fellow soldiers. Discussion with the anesthetist onboard led to the idea of establishing walking blood banks further forward. But would it be safe to be a soldier and blood donor simultaneously? Investigations on how a standard blood donation affected combat readiness skills were initiated as soon as the mission ended. The surgical team's anesthetist was head-hunted to the Senior Medical Officer (SMO) position for NORNAVSOC, and I prepared to enter medical school.

On the 2nd of May 2010, another SOF team was deployed to northern Afghanistan, comprising soldiers from Norwegian coastal rangers and NORNAVSOC. At about 14.00 local time, enemies took them under fire during a reconnaissance mission. Two hours into the firefight, two of the team members were injured. Soldier one was hit and instantly paralyzed as the bullet injured his spinal cord (9). Soldier two moved forward to retrieve Soldier one to a safe place. In this act, he was shot in the back.

The bullet had entered his lower back, beneath his armor, and traveled through his abdomen and chest before exiting two centimeters to the right of the left mamilla. The medic on the scene examined Soldier two, did minimal interventions, and moved him to the front right seat of their armored vehicle while the firefight continued (10). When the attack slowed down a bit, the team managed to secure a stronghold in a compound nearby. Soldiers one and two were moved inside. Soldier two walked himself, bleeding, in severe pain, and awake but confused (9). He describes looking down at his left chest and seeing flesh, blood, and something yellow and beating, thinking that it must be the heart (10). After further medical examination in the compound, it was evident that Soldier two was deteriorating and was suffering from non-compressible abdominal and thoracic bleeding. The Team Commander was on coms with the helicopter evacuation team. Their orders denied them to land in an area with an ongoing firefight. The Team Commander, a former medic, understood his team members' critical situation and relayed this persuasively to the aircrew. They understood the urgent situation, defied their orders, and landed (9). Soldier one was carried, and Soldier two walked with support to the helicopter. Four minutes after take-off, Soldier two was unconscious. Minutes later, he was at the surgical facility in Meymanah with no measurable vital signs. A laparotomy was done in the clinic's reception area, and resuscitation with blood products was initiated. Today, Soldiers one and two are back on duty in the Norwegian Armed Forces (9, 10, 11).

This incident shows how bravery, risk-willing colleagues, and sound clinical judgment saved two lives. Likely, only the slightest delay from the point of injury until surgery would have been detrimental, at least for Soldier two. Earlier blood transfusion could have improved survival chances with a delayed evacuation.

The reports from Afghanistan underpinned the importance of making blood and blood products available in an austere environment. A collaboration between the Blood Bank at Haukeland University Hospital in Bergen and NORNAVSOC was established. The research group Blood Far Forward was formed under the Department of Clinical Science at the Medical Faculty of the University of Bergen and the Department of Immunology and Transfusion Medicine at Haukeland

University Hospital. Professor Tor Hervig was imperative in this process, understanding the need for an unconventional approach to secure blood supply in austere environments. Internationally a paradigm shift in treating hemorrhagic shock started (12, 13). Drs Philip Spinella and Geir Strandenes established an international research network: Trauma, Haemostasis, and Oxygenation Research Network, to promote research on the field and held the first meeting in Bergen, Norway, in 2011 (14). While studying medicine, I also contributed to other relevant research (15, 16, 17, 18, 19, 20, 21, 22) and educated medics in activating walking blood banks in NORNAVSOC. I am currently the Senior Medical Officer at NORNAVSOC, part-time in family medicine, part of the Norwegian Blood Coordination Center, and a member of the THOR steering committee.

This thesis reflects a body of unique academic and applied work conducted by our research network. Through working on this project, I have gained awareness about how medical truths have an expiration date, and like fashion, old ideas are rejuvenated in cycles. Therefore, the introduction starts with a brief historical overview.

1.2 Re-learning history

The discovery of whole blood

Transfusion medicine is not a novel idea. In the early 19th century, obstetrician James Blundell did the first published lifesaving blood transfusion, where he transfused a female dying from post-partum bleeding with blood from her husband (23).

Military and civilian transfusion medicine have developed hand in hand. The academic developments in transfusion medicine have led to changes in military practices. Large-scale trauma care and transfusions during the wars have provided knowledge, clinical experience, and interventions beneficial for civilian health care. Dr. Robertson and Dr. Watson wrote in 1917 that “under the stimulus of war, and the mass of material war provides, our methods will steadily improve” (24).

The first large-scale successful use of whole blood for the resuscitation of hemorrhagic patients was during World War I (WWI) when Canadian physician Lawrence Bruce Robertson and American physician Oswald Hope Robinson introduced whole blood transfusion. Later, their achievements were described as the "Most important Medical Advance of the War" (25). In the early 20th century, there were no means of storing blood. Transfusion was done with the donor bedside to the patient, and whenever a patient needed a blood transfusion, a suitable donor had to be found, often a family member (26). Different equipment and techniques for direct transfusion were developed and discussed (27). Sodium citrate as an anticoagulant gained popularity and facilitated a separation between the donor and recipient in space and time. Initially, storage was not recommended for more than hours after the donation, preferably in warm water (27).

One of the earliest known blood bank initiatives was by Percy Lane Oliver in London in 1921. He acknowledged the problems of tracking down a suitable donor once the need for blood occurred. To ease this situation, he established the first known volunteer donor panel such that these could be contacted when fresh blood was needed. London Red Cross Blood Transfusion Service was established, and Mr. Oliver ran the service from his home (26). This service grew to more than 50 donor panels spread across Great Britain by 1939. The idea also spread to other countries, including Austria, Japan, Germany, Belgium, Russia, France, and Siam, where donor panels were recruited and served local hospitals on short notice. Most of these panels were volunteer and unpaid donors. In London, in 1938, Janet Vaughan took the initiative to plan for establishing a blood depot based on the unstable global situation. On September 1st, 1939, she got a letter from the Medical Research Council saying, "Start bleeding." (26).

Whole blood was the primary resuscitation fluid during World War II (WWII), the Korean War, and the Vietnam War - with good outcomes. Blood was supplied domestically from the regular blood collection stations and locally through walking blood banks at treatment facilities on the battlefield (28).

The U.S. Military Blood Program collected and transfused approximately 400,000 units of whole blood from the 1940s to the 1960s (29), and during the Vietnam War, close to one million units were transfused (5).

Shifting away from whole blood

In the first decade after WWII, walking blood banks transitioned from being part of the primary blood supply source to mainly be part of preparedness plans. During the Cold War, the US government in Utah and Indiana initiated a large-scale blood typing and screening program for all their citizens, including children down to the 5th grade, as an emergency preparedness plan in case of an atomic attack. About 1,5 million donors were screened. To avoid ABO mismatch, qualified donors were offered to tattoo their blood group on the right side of the chest; hence the initiative was nicknamed the Tat-Type program (3). Elderly people in Bergen also report that during their blood donor career in the 1960s, they were called for emergent vein-to-vein transfusion with the patient behind a curtain (30).

The depiction of Benziger et al. on how they solved blood banking in a small blood bank in Montrose Memorial Hospital, Colorado, USA, is a rare example from the 1970s of the successful use of walking blood banks. They only kept a minimal inventory to reduce wastage and relied on a walking blood bank for quick supply upon demand (1).

As time passed from the last war and transfusion-related infections caught attention, efforts to prevent them were applied. An example of this is a case report from a newborn ICU in Jackson, Mississippi, USA, in 1979 describes how 205 transfusions from 72 walking donors were successful except for one case with the fatal transmission of hepatitis. Therefore, the authors recommended discontinuing walking blood banking (31).

The first case of Acquired Immune Deficiency Syndrome (AIDS) was reported in 1981, but the Human Immunodeficiency Virus (HIV) was not discovered until 1984.

In the early 1980s, thousands of patients were infected with HIV through transfusion of blood products (32).

As transfusions strategies shifted from whole blood to component therapy and concerns about transfusion-transmitted diseases increased after the HIV epidemic, walking blood banks became increasingly uncommon.

In 1980 Carrico et al. published a study that promoted the use of balanced saltwater solutions for patients suffering from hemorrhagic shock (33), a solution without the risk of transfusion-transmitted disease. An era of a balanced salt solution for massive bleeding began, and walking blood banks disappeared even further.

American warships still depended on walking blood banks due to logistical hurdles and as an emergent solution to a crisis. A case report from a US Aircraft carrier from 2003 describes how walking donors saved a sailor's life. The patient suffered from rectal bleeding due to a Meckel diverticulum, and the vessel was too far from shore to evacuate. The patient survived after receiving warm fresh whole blood from colleagues on the ship. The authors also describe how walking blood banks are planned and screened and how equipment is stored for emergency use only (2).

From the late 1970s to the early 2000s, the use of walking blood banks was rare or nonexistent until 2001, when a terrorist attack on the World Trade Center again started a war.

Re-introducing whole blood

In 2003 an American casualty support hospital (CSH) was deployed to Baghdad, Iraq, during Operation Iraqi Freedom. After deployment, Major James Sebesta and colleagues summarized their lessons learned in a report published in 2006 (34). Among other lessons, using an emergency donor panel was described as a success after donating and transfusing more than 500 units over six months for the most severely wounded. The surgeons describe warm fresh whole blood as a “magic bullet” for physiologically exhausted patients. Not very different from descriptions after WWI, about 90 years earlier (24).

The Royal Caribbean Cruise lines have used emergency walking donors on board their cruise ships since 2008 (35). In 2010 NORNAVSOC planned to make whole blood available in austere environments (17). In 2014 Jenkins et al. reported that walking donors were utilized in rural Minnesota on a program designed by Mayo Clinic to ensure the highest level of care, also far from a level 1 hospital (36). A paper from 2015 describes how a multinational walking blood bank was established at the Kabul International Airport military base on a French initiative. Between June and October 2011, more than 3500 possible donors were identified, and 93 units of whole blood were collected for emergency transfusion (37). In the French military walking donors have been incorporated since 2017. One of their main concerns when implementing this system was the soldiers' performance after blood donation (38).

Haukeland University Hospital, a level one trauma center in Bergen, Norway, established a contingency plan for a mass-casualty event in 2016 based on walking donors (39). In 2019 this blood bank was activated when a trauma patient arrived at the hospital and drained the inventory of the blood banks in a few hours. The patient received nearly 200 whole blood and blood component units, and it took 17 days to restock the blood bank inventory. One of the lessons learned was that it takes time until the blood is ready for transfusion after activating the walking blood bank. Kaada et al. suggest that recruiting hospital staff as walking donors could shorten this response time (40). In 2020 Braverman et al. described how whole blood emergency donor pools are organized in Texas, USA (41). In 2021 international colleagues collaborated on developing and recommending an emergency plan for massively bleeding patients when blood bank inventory is low. This group, led by Dr. Holcomb, stated that it is better to have a well-thought-out and trained plan rather than trying to develop a hasty plan during a disaster (41).

Different guidelines now recommend whole blood or reconstituted whole blood in a ratio of 1:1:1 for resuscitation of hemorrhagic shock in trauma (42, 43, 44). The body of evidence that blood transfusion is better for hemorrhagic trauma patients than an infusion of crystalloids is increasing (45). Whether whole blood is better or equal to component therapy is still under investigation (46).

On the national level, Norway recommends using whole blood for massive bleeding in “The national trauma plan” from 2020. Thus whole-blood-based resuscitation is on the rise as the preferred fluid for hemorrhagic shock patients in many countries (47).

As whole blood from walking blood banks is re-entering the pre-hospital arena, discussing what’s unique about pre-hospital medicine and blood banking is appropriate.

1.3 The pre-hospital environment

The term “Pre-hospital medicine” covers patient care from the point of injury or debut of disease until arrival at a hospital. Disease and trauma are no different pre- and in-hospital, but the resources and the environment are (48).

Limited resources and sub-optimal work conditions are the most important limitations in pre-hospital care. A backpack can only carry limited medical supplies, and the contents must be well-prioritized. Care is provided under changing weather, traffic, crowds, challenging terrain, and tactical situations in the military (48).

The spectrum of pre-hospital services includes ambulance services in cities, helicopter emergency medical services, the medic on a military mission, remote clinics, surgical facilities, and primary care units. The austere environment is often used when referring to remote pre-hospital situations, far-forward military and expeditionary medicine and is characterized by severe logistical constraints.

Whole blood stored in walking blood banks can be the only logistic feasible method for making whole blood available in the austere environment. Component therapy is complicated far forward due to the three blood components' different storage requirements. Red blood cells must be refrigerated, plasma stored frozen, and platelets stored at room temperature under constant agitation (49). Thus, this is only feasible at a fixed facility with electricity, light, and heating.

1.4 Walking blood banks as preparedness plans

In 2010 NORNAVSOC established walking blood banks by recruiting their SOF soldiers as blood donors and thus made whole blood transfusion possible on remote missions. Contemporary, this was unorthodox and met resistance. At the time, whole blood was not a regular inventory of Norwegian blood banks, and the use of whole blood outside the hospital was nonexistent.

The 75th ranger Regiment of the United States Army early copied the NORNAVSOC approach and operationalized the regiment as walking donors banks (50). In the civilian world, a large oil and gas company in Norway established walking blood banks on their most remote offshore oil installations. The Royal Caribbean Cruise Liners have had walking blood banks onboard since 2008 (35).

In Norway, it is stated in "Helseberedskapsloven," a national act on health care emergency preparedness, that all levels of the public health care systems shall provide their services in peace-, crisis- and wartime during the continuum of care from primary care through acute care to definite care in the specialized health care system (51). In Norway, all municipalities are responsible for primary health care for their inhabitants. Evacuation- and specialized healthcare services are under national control and decentralized through four regional health trusts: Helse Nord, Helse Midt-Norge, Helse Vest, and Helse Sør-øst. The national health care preparedness plan "Nasjonal Helseberedskapsplan" describes how preparedness should be planned and organized. The four core preparedness principles stated in this plan are:

- Responsibility for emergency preparedness lies with the service that provides the service under the normal situation.

- The conformity principle state that the operational organization in a crisis shall resemble the organization under a normal situation.

- The principle of proximity entails that crisis should be handled at the lowest systemic level possible.

- The principle of cooperation entails that each sector is responsible for a functional cooperative effort with relevant partners in a crisis. (52).

This concept is part of "Totalforsvarsmodellen," a joint military and civilian system that ensures mutual support and cooperation to prevent, plan, and handle crises.

Norwegian Coordination center for blood supply at Haukeland University Hospital in Bergen, Norway, has launched a program, "Finnmarkspiloten," to investigate the feasibility of establishing local walking blood banks in rural communities in northern Norway. The principles are similar to the NORNAVSOC method, where the local population is recruited as regular blood donors and first bleeds when blood needs appear (53). Also similar to Oliver Percy Lane's *donors on the hoof* in London in 1921, (26).

Berlevåg, an isolated fisherman village far north of Norway, implemented a walking blood bank in their preparedness plans during the fall of 2022 as a part of "Finnmarkspiloten." On 21.01.23, the first-ever national activation of a municipality walking blood bank happened in Berlevåg when a patient suffering from a suspected ruptured aortic aneurysm presented at the local emergency clinic. Activation of the blood bank was successful, and one unit was donated. Due to an uncertain diagnosis, the unit was not transfused but followed the patient on the evacuation (54).

1.5 Risk mitigation in blood banking and blood transfusion

Side effects for the patient

The two adverse events blood bankers try to avoid are:

1. Major ABO mismatch causing deadly hemolytic transfusion reaction.
2. Transfusion transmittable disease.

Blood banks have a rigorous system to avoid these side effects. Donor selection, voluntary donors, donor screening, pre-donation interviews, testing of blood post-donation, blood product processing, and pre-transfusion cross-matching of the donor

and recipient's blood are some of these measured to increase safety for the patient (55). Donor selection includes age and weight limitations, screening for medical conditions, and donation day screening of vital signs and hemoglobin levels. Donations are executed in a room designed for the purpose and are monitored by qualified personnel (56).

Side effects for the donor

The British national hemovigilance system: Serious Hazards of Transfusion (SHOT) reports adverse blood donation and transfusion events annually. In 2021 there were 54 serious adverse events reported from more than 1,8 million donations. This equates to one incident per 38781 donations, and include hospitalization, secondary injuries after fainting, and nerve and tendon injuries (55). Blood donors more commonly experience soft tissue injuries and vasovagal reactions (56). Vasovagal reactions occur in 2-5% of donations, with syncope in less than 0.3% (57, 58, 59, 60, 61). The vasovagal reaction most often occurs during or immediately post-donation. However, delayed reactions are reported up to 24 hours post-donation (62).

The Norwegian hemovigilance System (TROLL) summarized their reports after the first ten years of reporting from 2004 to 2014. In approximately 2.2 million blood and apheresis donations, they received 2564 reports on adverse events, equivalent to 134 reports per 100.000 donations. Most of the reports were on local irritation of the puncture site. Other events were vasovagal reactions, hematomas, pain in the arm, and more. 77 of the incidents led to hospitalization. Syncope occurred in approximately 0.04% of the total donations and 22% of the 839 syncope were delayed and occurred after the donor had left the blood bank (63).

Norwegian blood donor advice includes: Eating and drinking before donation, avoiding donating if you are tired or stressed, resting immediately after donation, and avoiding exertive activity the first 24 hours after donation (63).

The American Red Cross Blood Service similarly advises donors to be well-rested and hydrated on donation day and avoid heavy lifting and vigorous exercise the same day they donate blood (64).

The British blood service, NHS Blood and Transplant, does not include general advice to refrain from heavy exercise after a blood donation (65).

To avoid potential harm following syncope, some organizations advise personnel with a hazardous occupation, i.e., emergency services, are requested not to resume work for at least 24 hours after donation (56, 64) There are even stricter regulations for flying personnel with a 72-hour restriction period (66).

Syncope is rare but probably the most critical adverse event associated with walking blood banks. Research on reducing vasovagal reactions is ongoing. An important paper will be the Strategies to Improve Donor Experience Study by The National Institute for Health and Care Research Blood and Transplant Research Unit in Donor Health and Behaviour in Great Britain, expected in the summer of 2023.

1.5.1 Walking blood bank risk mitigation and side effects

Walking blood bank planning and preparation should follow the regular blood donor recruitment guidelines. Including donor selection between volunteer donors, medical screening, blood group testing, and infectious disease screening. Pre-donation interviewing is also possible.

When a walking donor has donated blood, it can be transfused immediately, stored at room temperature for up to 24 hours before being discarded or refrigerated within 8 hours, and stored for up to 35 days (13). This immediate aspect differentiates and imposes risks in walking blood banks compared to regular blood banking for both the recipient and donor. Pre-transfusion blood group and antigen screening of the patient is challenging and dependent on the situation. As is a pre-transfusion screening of donors for infectious disease or double-checking donated blood`s ABO group. Cross-matching of donor and recipient`s blood is also difficult. One can argue that cross-matching and rapid testing of blood groups can be done pre-hospital with field test

kits like the French military protocol (38). Still, it is essential to acknowledge that this is a stressful situation for both the donor and the medical provider on the scene. Stress increases human error rates, and uncertain lab results could possibly confuse the provider (67).

From the patient's perspective, the abovementioned risks must be weighed against the risk of not receiving a transfusion. Mortality in severe traumatic hemorrhage is high and increases with prolonged evacuation (68). In such situations, it is possible to imagine that recipients will accept the risk of receiving the transfusions compared to the risk of not receiving one.

In a walking blood bank setting, the donor can either be in a critical situation already or needs to return to essential tasks after the donation. Hence, the donor is possibly in a hazardous situation before, during, and immediately after the donation. In a military setting, the donor could also be the next patient; if so, the patient suffers the trauma with 450mL blood less to bleed.

To inform discussion on donor safety further, the relevant physiological aspects of this thesis need to be presented.

1.6 Physiological aspects

1.6.1 Cardiovascular effects of blood donation

The overall goal of the cardiovascular system is to deliver oxygen and nutrients to and remove waste products from the tissues. The main denominator for oxygen delivery is cardiac output and blood oxygen content (69).

The cardiovascular system is complex and has several regulative mechanisms to retain cardiac output and oxygen delivery. The immediate response to blood donation is the sympathetic increase of cardiac output, vascular resistance, and fluid shift from the interstitium to the vascular bed mediated by Starling forces (70). Hours after bleeding, the Renin-angiotensin-aldosterone system (RAAS) has effects as described below (69).

Lost volume results in reduced venous return to the right atrium and ventricle. According to Fick´s principle, the venous return to the right side of the heart determines cardiac output from the left ventricle.

Fick´s principle determines cardiac output by oxygen absorption per time and arteriovenous oxygen difference. Derived from Fick's principle is the following equation that determines the delivery of oxygen to the tissues:

$VO_2 = CO \times ([Hb] \times 1.34 \times SaO2 + 0.003 \times pO2)$

VO_2	Oxygen consumption in mL per time
CO	Cardiac output determined by stroke volume x heart rate.
[Hb]	Hemoglobin concentration in the blood in g/dL.
1.34	is known as the Hufners constant and is the maximal oxygen-carrying. capacity in mL per gram of hemoglobin.
SaO_2	is the oxygen saturation of the hemoglobin percent.
0.003	is the amount of soluble oxygen in the plasma at a given partial pressure in mL per mmHg.
pO_2	is the partial pressure of oxygen in the blood (0.023 mmHg at sea level) (71).

With acute bleeding, baroreceptors sense reduced blood pressure in the aortic arch and carotid sinus. These baroreceptors signal through the 9^{th} and 10^{th} cranial nerve to the nucleus tractus solitarius in the medulla, subsequently stimulating the vasomotor center and inhibiting the vagal center in the medulla. The net effect of these actions is increased cardiac output through increased inotropic and chronotropic action of the heart and increased tone in arterial and venous vascular beds that increase venous return. The vasomotor center also stimulates the adrenal glands to produce more adrenalin and nor adrenalin to the systemic circulation, enhancing the global sympathetic response (69).

Another immediate effect blood donation is recruiting extravascular fluid to the vascular space. This process is driven by oncotic and hydrostatic mechanisms known as Starling forces. First, reduced hydrostatic pressure in the capillaries shifts water into the vasculature. Secondly, overlapping with the water in flux, proteins are shifted to the vasculature to regain plasma oncotic pressure (72). This process is fast. Saito et al. suggest that about 200mL of fluid is replaced during a regular blood donation and that after ten more minutes, the complete volume depleted is restored (70).

A slower response to bleeding is the RAAS which is in effect hours to days after donation. In this system, the juxta glomerular apparatus sense reduced pressure in the glomeruli afferent arteriole, reduced sodium concentration in the distal convoluted tubule, and secrete renin into the systemic circulation. Beta-1 receptors also augment renin secretion in the same area. In the systemic circulation, renin converts angiotensinogen to angiotensin 1, which angiotensin-converting enzyme converts to angiotensin 2 in the pulmonary capillaries. Angiotensin 2 is a steroid hormone with several effects. It causes vasoconstriction in venous and capillary beds, stimulates thirst through the hypothalamus, and increases noradrenalin secretion at postganglionic sympathetic fibers increasing the sympathetic response. Angiotensin 2 also stimulates aldosterone production in the adrenal glands, which promotes salt and water retention through changed gene expression in the nephron tubule (69).

1.6.2 Hematologic effects of blood donation

[Hb] in the blood is affected by blood donation. A blood donation of 450mL is about 10% of an adult's total blood volume and about 10% of the circulating hemoglobin. Immediately post-donation, [Hb] is relatively maintained because the lost hemoglobin corresponds to the total lost volume (73). A response to volume depletion is recruiting extravascular fluid to the circulation. This response is mainly mediated by arterial baroreceptors when the carotid sinuses censor a drop in cardiac output. Hours after donation, the volume is likely restored (74). Restoration of lost hemoglobin is slower; thus, [Hb] is reduced when the volume is restored. Pottgeisser found that the mean time for restoration of lost hemoglobin after a 550mL blood donation is 36 +/- 11 days (75). Regulation of [Hb] is primarily mediated by the hormone erythropoietin

(EPO) (76), and a standard blood donation has been shown to increase circulating EPO significantly (75).

Excess iron leads to harmful reactive oxygen species; therefore, iron homeostasis is delicately regulated. The downside of this is vulnerability to iron depletion. The primary consumer of iron is hemoglobin synthesis. Hence, depleted iron stores will decrease hemoglobin levels (77). Iron depletion anemia is well known to reduce physical endurance both through the reduction of oxygen-carrying capacity and the tissue iron depletion itself by reduced oxidative capacity in muscle tissue (78, 79). Some also suggest that iron deficiency causes reduced cognitive capacity (78). A regular blood donation (450mL) contains about 250mg of iron (0.5mg/mL). This equals about 30% of the male and up to 80% of the female total iron storage. Iron storage is depleted after a regular blood donation, and the time to replenish red blood cells is probably increased with iron deficiency (75).

1.6.3 Cognitive effects of volume depletion

Cessation of oxygen delivery to the brain causes loss of consciousness in five to ten seconds. Since the brain is enclosed in a rigid container (the skull), changes in blood volume affect intracranial pressure (ICP) and, thus, blood flow to the brain. Comprising only 2% of the body weight, the brain receives about 15% of the resting cardiac output (69).

As abnormalities in blood flow or oxygen delivery have an immediate and detrimental effect on brain function, cerebral blood flow is well regulated. Autoregulation is multifactorial and reacts to changes in systemic blood pressure to maintain the required cerebral blood flow (80). The postural change of standing up from lying down shifts about 500mL of blood from the central regions to the lower extremities. This shift decreases venous return and cardiac output and thus lowers systemic blood pressure. Through baroreceptors in the large arteries and activation of the sympathetic system, blood pressure is restored within 30 to 40 seconds. Feeling dizzy, light-headed, or even syncope after quickly getting up is an expression of lacking buffering capacity in autoregulating cerebral blood flow to counteract the

rapidly decreased systemic blood pressure. This example shows that regulating cerebral blood flow is more vulnerable to rapid changes in systemic blood pressure. Prolonged changes in blood pressure are well compensated by cerebral blood flow within the limits of 50mmHg to 150mmHg (80).

Menke et al. found through near-infrared spectroscopy that during a regular blood donation of 450mL cerebral blood volume increased by about 7,5%, and cerebral oxygenation was maintained within normal parameters (81).

1.6.4 Physiological response to exercise

Adenosine triphosphate (ATP) is the energy source for muscle contraction. Three systems produce ATP during exercise: The phosphocreatine, glycogen-lactic acid, and aerobic systems (69). Their main difference lies in the speed and duration of regeneration of ATP from amino di- and monophosphate in the muscle mitochondria.

1) The phosphocreatine system generates the quickest and most extensive amounts of ATP and produces 4 mol per minute but lasts only for up to 10 seconds.
2) The glycogen-lactic acid or anaerobic system provides energy for ATP regeneration through non-oxidative ATP generation from glycolysis of glycogen and pyruvate degeneration to lactic acid. Compared to the phosphocreatine system, it can produce about 2 mol of ATP per minute, and under ideal circumstances, this process can last for about 1.3 – 1.6 minutes.
3) The aerobic system is the oxidative process of the nutrients: glucose, fatty acids, and amino acids in the muscle mitochondria. This process is oxygen dependent, produces up to 1 mol of ATP per minute, and last as long as the nutrients last, i.e hours to days.

The phosphocreatine system is used for sprints up to 10 seconds, 100-meter dash, weightlifting, etc. The glycogen-lactic acid system for 400-meter sprints, 100-meter swims, tennis, etc., and the aerobic system for 10,000-meter runs and longer. Some activity often combines the different systems for ATP generation, such as 2000-meter rowing, 1500-meter running, and 400-meter swims that rely on glycogen-lactate

generation combined with aerobic nutrient oxidation. The body harmonizes the three systems to deliver sufficient ATP for the required workload. All three pathways reconstitute each other during and after an exercise by reverse activation order. The aerobic system reconstitutes the glycogen-lactate system, which then reconstitutes the phosphocreatine system. These recovery mechanisms form the basis of the oxygen debt concept. The oxygen reserve for aerobic metabolism without breathing new oxygen is about 2 liters. It is stored in the lungs, the hemoglobin, the bodily fluids, and the muscle fibers. During heavy exercise, when oxygen demand exceeds oxygen delivery, stored oxygen is rapidly depleted, and anaerobic metabolism produces ATP. After the exercise, extra oxygen is needed to restore the energy systems and replenish the stored oxygen. The body is in oxygen debt (69). Blood lactate acid levels increases during heavy exercise as a response to the anaerobic metabolism, and blood lactate concentration measures the degree of anaerobic metabolism. After exercise, concentrations quickly return to normal levels, often within minutes if oxygen is available (82).

During exercise, oxygen consumption increases dramatically. At the resting state, a young male weighing 80 kg consumes about 250ml of oxygen per minute. A marathon athlete, during heavy exercise, can consume up to 5100mL of oxygen per minute, a 20-fold increase. As oxygen stored in the body is limited, oxygen consumption is restricted to oxygen delivery. The respiratory system has a 50% safety margin between demands at maximal exercise and actual maximal breathing capacity. Thus, the respiratory system is not the limiting factor in oxygen delivery for a healthy person. Hemoglobin levels are static during adult life (83) unless triggered to adapt to environmental conditions or pathological or pharmacological stimuli (69). Thus, Hemoglobin limits oxygen delivery but cannot adapt during exercise.

The major player in determining oxygen delivery capacity is the flow of oxygen-carrying blood to the tissues, known as cardiac output. Stroke volume by heartbeat equals the cardiac output, and the flow can vary from 5,5 L/min in the resting state to 30 L/min or more per minute in fit persons. During heavy exercise, metabolic, hormonal, and neuronal signaling increase cardiac output by an increased venous

return to the heart, increased inotropic and chronotropic action of the heart and increased blood pressure. During heavy exercise, stroke volume increase by about 50%, and heart rate increase up to 270% from the resting state, and by the time stroke volume has maximized, heart rate has only increased halfway to maximal heart frequency (69).

Maximal oxygen consumption (VO_{2MAX}) is determined as oxygen consumed by the cells per time unit. Since the cells cannot utilize more oxygen than the cardiovascular system supplies, oxygen consumption equals oxygen delivery, and the major limiting factor is cardiac output. Maximal stroke volume is obtained earlier than maximal heart rate, at about 50% of maximal cardiac output (84). Thus, heart rate can indicate cardiac output during heavy exercise, especially in anaerobic exercise, approximating maximal effort (69).

1.7 Testing performance

1.7.1 Testing of physical performance

Over the last 25 years, Hill`s 100-year-old theory that maximal oxygen uptake is the primary denominator of fatigue has been debated by Noakes et al., who propose an alternative model for fatigue: The central governor model (85). While Hill`s model explains fatigue and maximal exercise cessation by a ceiling effect of oxygen uptake followed by anaerobic metabolism (86), Noakes argues that there is a feeling of fatigue originating in the encephalon preventing a catastrophic homeostasis failure that causes a cessation in maximal exercise. The common belief in exercise physiology is that Hill`s theory is still valid. Noakes's theory offers an alternative theory based on new interpretations of historical data without a method to validate the new theory (87). Therefore, this thesis's rationale for exercise physiology is based on Hill`s theory.

Physical fitness is defined as “A person`s ability to work effectively, enjoy leisure time, be healthy, resist hypo-kinetic disease or condition, and meet emergencies.”(88). Physical fitness is multidimensional, including performance and

health aspects. Cardiorespiratory performance is one of the main components of physical fitness, in addition to muscular endurance, strength, flexibility, and body composition (89). Hill and colleagues postulated in 1923 that the cardiorespiratory system's maximal oxygen delivery capacity (VO_{2MAX}) determines the body's maximum oxygen consumption capacity (86). VO_{2MAX} is the maximum amount of oxygen a person can deliver to the tissues despite an increased workload (88).

The World Health Organization defined VO_{2MAX} as the reference for cardiorespiratory fitness in 1967 (90). Hill`s theory is still the leading concept and gold standard for assessing maximal cardio-respiratory endurance (88). VO_{2MAX} is expressed either in absolute values as liter O_2 per minute ($_{ABS}VO_{2MAX}$) or relative to body weight as mL per kg per minute ($_{REL}VO_{2MAX}$) (88). Determination of VO_{2MAX} is commonly done by treadmill or ergometer bike and fixed protocols of timed incremental workload until volatile exhaustion. Determination can be either direct or indirect, and direct measure is more accurate and resource dependent. An indirect measure of VO_{2MAX} is done by estimating oxygen consumption based on heart rate and time lapsed in a fixed incremental workload protocol. Direct measurement of VO_{2MAX} is done by analyzing inspiratory and expiratory gasses for CO_2 and O_2 in a breath by breath analyzer (88). Criteria for determining VO_{2MAX} is an area of debate. Still, practice today is either reaching a plateau of oxygen consumption defined by a flat curve despite increased workload or reaching a respiratory exchange ratio of 1.15 or above or blood lactate concentrations above 8 mmol/l (84).

Measurements of direct VO_{2MAX} are highly valid and reliable. On the other hand, indirect measures of VO_{2MAX} are estimates and inaccurate. The advantage of the indirect method is cost-effectiveness (88).

1.7.2 Testing of cognitive performance

Executive functions allow humans to think, be creative in problem-solving, resist temptations, stay focused, and play with ideas. Highly important skills in emergencies and crises.

The core executive functions are:

Inhibition – The ability to resist temptation, maintaining self-control, preventing impulsive acts and cognition, and keeping attention to a task.

Working memory – The short-term memory needed to solve an immediate task.

Cognitive flexibility – The ability to think outside of the box, seeing things from a different perspective, and adapting to changing circumstances (91).

Executive functions are essential for various reasons: mental health, physical health, quality of life, school readiness and success, job success, marital harmony, and public safety. Reduced executive functions will, in the latter example, lead to social problems like crime, violence, and emotional outbursts (91). Normand and Shallice have elaborated on the involvement of executive functions in tasks that are not automated and emphasize five situations:

1. Planning and decision making
2. Error correction or troubleshooting
3. Novel sequences of actions that are not well rehearsed
4. Dangerous or technically difficult situations
5. Resisting temptation or overcoming strong habitual response (92).

The anatomical domains for executive functions are in the brain's prefrontal cortex. Various tests and test batteries exist for the different executive functions, and a test typically assesses one of the executive functions (93). Executive functions are commonly investigated for attention deficit and hyperactive disorder (ADHD) and evaluation of neurocognitive dysfunction, especially in elders. A systematic review of the most frequently tested executive functions domains from 2009 – 2014 in assessing mild cognitive impairment showed distribution in descending order: mental flexibility, verbal fluency, planning, working memory, and inhibitory control (93).

1.8 Why is this thesis needed?

Blood transfusions and blood banking are often regarded as “planned activities.” Walking blood banks is a plan for unforeseen incidents and presents increased risks

compared to conventional blood donor panels. The Blood Care Foundation and the US Navy describe problems with walking blood banks in rural areas being the risk of transmitting infections due to lacking screening capabilities, scarce resources in a small community, and the social aspects of being rejected as a donor due to high-risk behavior are the main problems (94). However, walking blood banks are an essential resilience measure that has been used extensively in the post-2000 conflicts of the Middle East with good outcomes (37, 95, 96). Walking blood banks are also proposed as the solution to civilian blood-preparedness plans in austere locations (95, 97, 98) and following disasters.

1.8.1 Is it safe to be a walking donor?

The first published concern about the reduced physical performance after phlebotomy dates to 1942 and reported athletes performing under par only a few days after blood donation. This concern led to a rule against athletes giving blood at Springfield College in Massachusetts in USA (99).

Physical performance after blood donation has been investigated at least 20 times with different methods, aims, study groups, and findings (73, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, 111, 112). There have also been two systematic reviews (113, 114), one of which has been criticized (115). Seven relevant articles, apart from those in this thesis, have investigated the immediate effects after phlebotomy (73, 100, 104, 107, 108, 111, 112). Results vary, and most study groups are small and homogenous, often young athletes. The two reviews conclude with a 4-15% decreased aerobic performance. Cognitive performance was not present in the literature before this project started. In 2020 Nadler et al. published that the combat skills of Israeli soldiers were maintained 1 hour after blood donation, as were cognitive and anaerobic performance (22)

Based on this, it is fair to say that the body of evidence on performance immediately after blood donation needs further investigation. Reintroducing walking blood banks yields higher resolution on the donor safety aspect and post-donation care. *Donors on*

the hoof will return to their duty after donation; we owe them a scientific basis for proper advice on post-donation measures.

Safety concerns about the donor are not new. During WWII, Dr. Forrest Lowry reports in his diary in February 1943 at a surgical aid station in Gafsa, Tunisia: "Blood is so precious, so urgently needed! What we do give is being obtained from our personnel who are most willing, but they need it themselves after putting in long hours without rest or sleep".

Balke et al. had the same concern about 70 years ago. They expressed it like this: "Practical experience gained in the course of a large number of blood donations in recent years has proved that the loss of about one pint of blood is of no serious consequence to the average healthy adult, provided that no extraordinary demands are made on the donor in the form of physical exertion or environmental stress. Nevertheless, responsible medical personnel should be able to advise blood donors whether it is necessary and, if so, for how long it is recommended to refrain from strenuous or exacting occupational or recreational activities." (116)

A basic rule of medicine is: "Not harm." Essentially this is all the argument needed to execute this project. Are we putting voluntary blood donors at risk when asking them to donate blood in a possibly unsafe environment? Most likely, yes, the obvious is that when you donate blood, you have 450mL less blood to bleed if you are injured. But what if your cognitive or physical performance is decreased? Could this put the donor in harm's way as well? As good medical providers, we must be able to inform voluntary blood donors about the possible risks they are exposing themselves to. Several questions needed to be answered: What is the net effect of blood donation on physical and cognitive performance? Will far-forward blood banks impose unethical risk on the donor?

2. Aim of the thesis

This thesis aimed to investigate whether it was safe to be a walking donor when the donor needed to return to a demanding task as soon as the donation was completed.

2.1 Hypothesis

We hypothesize that donating 450mL of whole blood does not significantly affect physical or cognitive performance immediately after donation.

2.2 Specific aims

1. Quantify a possible decrease in combat readiness skills within 30 minutes of blood donation in rested special forces soldiers.
2. Quantify a possible decrease in physical performance within 30 minutes of blood donation in fatigued and dehydrated special forces soldiers.
3. Quantify a possible decrease in physical and cognitive performance within 30 minutes of blood donation in regular blood donors.
4. Evaluate the possibility of teaching non-medics to perform a field blood donation.

3. Methods

This section will outline study designs, methods, population, interventions, outcome variables, data collection, and statistical methods. I refer to the respective papers for in-depth detail of each test and other technical details.

Ethics

Appropriate research governance and frameworks have been applied throughout all three studies. They were conducted according to the approved protocol, the Declaration of Helsinki, and the Principles of Good Clinical Practice. All donors were always under medical supervision.

The research ethics committee of the Regional West Health Trust approved Paper I in application numbers 2010/1559-11/REK (ID: 19998), Paper II in 2011/1239/REK ID: (26816), and Paper III in 2014/1927/REK (ID: 6687).

3.1 Paper I

Donor performance of combat readiness skills of special forces soldiers are maintained immediately after whole blood donation: a study to support the development of a prehospital fresh whole blood transfusion program

G. Strandenes, H. Skogrand, P. C. Spinella, T. Hervig and E. B. Rein

Transfusion 2013 Vol. 53 Issue 3 Pages 526-30

Design

A prospective, controlled clinical trial designed as a pilot study to support or defer a special forces walking blood bank, including a test for anaerobic fitness, strength, and soldier-specific physical and cognitive tests.

Method

Volunteer soldiers were assigned by availability to three groups and did baseline testing 1-5 days before the intervention and then re-testing immediately after donation. Results were compared to baseline tests.

Group 1 (n=7)	Aerobic fitness:
	Stepwise increase in speed and incline on a treadmill following the Bruce protocol until exhaustion using total belt time to determine VO_{2MAX} indirectly.
	Strength test:
	Maximum push-ups and maximum pull-ups.
Group 2 (n=12)	Cognitive performance:
	A standardized and familiar 50-round timed small arms shooting test.
Group 3 (n=6)	Soldier skill:
	A timed uphill walk with a 20 kg backpack through a known course.

All participants (n=25) were given a 60-minute training program to learn how to make a field blood donation.

Population

Twenty-five male active-duty special forces soldiers were recruited and randomized at availability.

Intervention

A regular blood donation of 450mL blood.

Outcome variables

Group 1	VO_{2MAX} reported in mL/kg/min
	Maximal heart rate in beats per minute
	Maximal capillary lactate in mmol/L

	Belt time in seconds
	Number of maximum push-ups
	Number of pull-ups
Group 2	Numeric score on the shooting test full score is 50 points.
Group 3	Timed walk of an up-hill trail in seconds
Field donation training	Number of attempts to get a field donation started.

Data collection

Data was collected manually by researchers and lab personnel and registered in an electronic database by the principal investigator.

Statistics

Group 1	Hodges-Lehman estimates of median difference.
Group 2	Paired t-test and two-tailed test. The level of significance was set at $p<0.05$. Data were reported using mean +/- standard error and median when appropriate.
Group 3	Not applicable.
Field donation training	The data were only described.

3.2 Paper II

Making whole blood available in austere medical environments: donor performance and safety

H. S. Eliassen, A. Aandstad, C. Bjerkvig, T. Fosse, T. A. Hervig, H. F. Pidcoke, et al.

Transfusion 2016 Vol. 56 Suppl 2 Pages S166-72

Design

A randomized, double-blinded clinical controlled trial designed to evaluate the immediate effects of a 450mL blood donation on physical performance in fatigued and dehydrated subjects.

Method

One group of Special forces soldiers did a baseline test for VO_{2MAX} before participating in a six-day escape and evasion exercise. The exercise-induced fatigue, dehydration, and sleep deprivation. Upon return from the exercise, the group immediately made a regular blood donation before re-testing VO_{2MAX}.

Population

All 13 participants in the exercise volunteered to join the study. Two participants failed to complete the exercise, and therefore only 11 participants were included in the final analysis.

Intervention

A blinded blood donation of 450 mL of blood.

Outcomes variables

The primary outcome was $_{REL}VO_{2MAX}$, measured in mL/kg/min.

Exercise tolerance time, measured in seconds.

Heart rate, measured in beats per minute.

[Hb], measured in g/dL.

Data collection

A VO_{2MAX} test lab with a treadmill and breath-by-breath analyzer was deployed to the exercise area. A professional test operator, blinded for the donation procedure, performed all VO_{2MAX} testing and recorded results continuously. The workload was increased stepwise according to the Bruce protocol.

Statistics

Differences within groups were analyzed with a paired t-test, and an unpaired t-test was used to find between-group differences. P-value <0.05 was considered statistically significant. Data were reported as means with a 95% confidence interval or one standard deviation.

3.3 Paper III

Immediate effects of blood donation on physical and cognitive performance a randomized controlled double-blinded trial

H. S. Eliassen, T. Hervig, S. Backlund, J. Sivertsen, V. V. Iversen, M. Kristoffersen, et al.

J Trauma Acute Care Surg 2018 Vol. 84 Issue 6S Suppl 1 Page S125-S131

Design

A randomized, controlled, double-blinded clinical trial designed to investigate the immediate effects of a regular blood donation on physical and cognitive performance in regular blood donors.

Method

By randomization, participants were assigned to either the intervention or control group. All met for testing three days within a 15-day cycle, with baseline testing on day 0, intervention and immediate re-testing on day 7, and re-testing on day 14. Three test cycles were arranged to complete all participants.

Cognitive testing was made by a comprised test battery, including the Trail-making test, Hopkins Verbal learning test, and the Stroop test was done before physical testing. A breath-by-breath analyzer determined VO2MAX while the candidate performed a stepwise protocol on an ergometer bike until volitional fatigue.

Venous blood was collected for [Hb] before and after testing on all test days.

Capillary lactate was analyzed at 0, 5, and 10 minutes after physical testing on all test days.

All testing, lab work, and blood donation were made at the facilities of Bergen University College with a consistent crew of researchers and lab workers from both the blood bank at Haukeland University Hospital and the physiological test laboratory at Bergen University College.

Population

1500 regular blood donors du for donation in the test period were invited by email. 68 were included in the trial, 36 in the control group, and 32 in the intervention group. 26 subjects completed all testing and met test criteria in the intervention group, and 31 candidates completed all testing and met test criteria in the control group.

Intervention

A standard blood donation of 450 mL blood. Both the candidate and the test operators were blinded for the donation procedure.

Outcomes variables

Maximal relative oxygen consumption $_{REL}VO_{2MAX}$, measured in mL/kg/min

Heart rate in beats per minute

Hemoglobin in g/dL

Lactate in mmol/L

The Hopkins Verbal Learning test score is measured in total and delayed scores.

The Trail-making test was timed, and the score was measured in seconds.

The Stroop test was timed, and the score was measured in seconds.

Details on the cognitive test battery

The Hopkins verbal learning test (HVLT) measured working and delayed memory and was introduced by Brandt in 1991. The original test did not include delayed memory. Benedict et al. revised HVLT to have a 25-minute delayed free recall trial, annotated as HVTL-R. In short, the candidate is orally presented with a list of 12 words three times before being challenged to identify the right words with a yes or no. In the delayed part, the candidate recalls as many words as possible from the list more than 25 minutes after the initial part. HVLT-R is a reliable test, and it was also found valid by Shapiro in 1999 (117).

Trail Making Test (TMT) comprises two tests, Trail Making Test – A (TMT-A) and Trail Making Test – B (TMT-B). TMT was developed as part of the Army Individual Test Battery in 1944 and is still commonly used to evaluate cognitive functions. Part A requires the candidate to draw a line between numbers 1 to 25 in ascending order. Part B requires the candidate to alternate between numbers and letters one at a time in ascending and alphabetic order. Both parts are timed, and this is the measure of performance. Reduced performance on TMT-A indicates substantial cognitive impairment, while performance on TMT-B assesses mental flexibility (118). In persons with reduced executive functions due to major depressive disorder, the Trail Making Test was reliable and suitable for sequential testing (119).

The Stroop color-word task is one of the world's most frequently used tests for attention interference. John Ridley Stroop developed the test in 1935 as part of his dissertation (120). Candidates are faced with three timed tasks, reading a list of colors written in black, reading a list of colors written in colored ink with another color than the written color, and last, the inhibition test where the candidates must name the color of the letters and not read the word they make. The Stroop phenomenon is well studied, and the test is considered reliable and valid for testing attention (121).

Data collection

Test operators manually documented scores continuously. The principal investigator collected and joined scores in an electronic database as they were ready.

Statistics

Student two-tailed t-test was used to analyze between-group differences, and a paired t-test was used to analyze within-group differences. The general linear model was used to analyze repeated measures. The significance level was set at $p<0.05$, and results were reported as mean +/- standard error of the mean.

4. Summary of the results

4.1 Paper I

Donor performance of combat readiness skills of special forces soldiers are maintained immediately after whole blood donation: a study to support the development of a prehospital fresh whole blood transfusion program.

Group 1 – Aerobic fitness

There was a non-significant decrease in $_{REL}VO_{2MAX}$ from 61.1 ± 3.7 ml/kg/min at baseline testing to 60.1 ± 3.4 mL/kg/min on donation day, p>0.05.

Maximal heart rate remained unchanged at 190 ±2.5 beats per minute at baseline to 190 ± 1.3 beats per minute on donation day, p>0.05.

Peak lactate level decreased but not significantly from 12.9 ± 8.8 mmol/L at baseline to 11.9 ± 8.5 mmol/L on donation day, p>0.05.

Strength testing did not reveal any difference on donation day compared to baseline results, with 15 ± 5.9 pullups and 50 ± 7.3 pushups at baseline to 14 ±4.9 pull-ups and 51 ± 8.2 push-ups on donation day, p>0.05.

Group 2 – Cognitive performance

The group performed slightly better but not significantly better on donation day, with a score of 35.3 ±1 at baseline to 37.1 ±1.7, p= 0.61.

Group 3 – Soldier skills

The group did the uphill walk in 35 minutes before and in 33 minutes after the donation. Measurements did not apply to statistics.

Field transfusion procedure

All candidates successfully drew one unit of blood from a colleague, and only one candidate needed two attempts, a 100% success rate. The median time for

phlebotomy was 6 minutes and 8 seconds. All candidates successfully placed a sternal intraosseous device and re-infused one unit of whole blood, also a 100% success rate with a median reinfusion time of 19 minutes and 30 seconds.

4.2 Paper II

Making whole blood available in austere medical environments: donor performance and safety

Group characteristics

Control and intervention groups were found to match in age, weight and VO_{2MAX} before the exercise. After the exercise donation group was significantly lighter than the donation group, 83.9kg to 84.6kg, $p<0.05$. Both groups had significant weight loss during the exercise. Were intervention group lost 3.8 kg, and the control group 2.8 kg, $p<0.05$.

Maximal oxygen consumption

The intervention group`s VO_{2MAX} declined significantly from baseline to donation day from ${}_{REL}VO_{2MAX}$ 56.0 to ${}_{REL}VO_{2MAX}$ 52.0 mL/kg/min and ${}_{ABS}VO_{2MAX}$ 4.91 to ${}_{ABS}VO_{2MAX}$ 4.36 L/min. A 7.1% decrease in ${}_{REL}VO_{2MAX}$ and 11.2% ${}_{ABS}VO_{2MAX}$, $p<0.05$.

Control groups VO_{2MAX} remained unchanged with 5.03 L/min to 4.85 L/min and 57.8 ml/kg/min to 57.8 mL/kg/min, $p>0.05$.

Between-group differences were significant on donation day, both absolute and relative values.

Exercise tolerance time

Exercise tolerance time (ETT) was significantly shorter (9,5%) in the intervention group on donation day compared to baseline testing, with a reduction from 968 seconds to 876 seconds, $p>0.05$. In the control group, there was a minor reduction in

ETT with a decrease from 970 seconds to 937 seconds, $p>0.05$, and the difference between the groups was not significant on any test day, $p>0.05$.

Heart rate

Submaximal heart rate increased significantly at each level of the Bruce protocol in the intervention group on donation day compared to baseline, $p<0.05$. We found no difference in sub-maximal heart rate in the control group on donation day compared to baseline, $p>0.05$.

Hemoglobin concentration

[Hb] decreased significantly in both groups from baseline to donation day. From 14.6 g/dl to 14.0 g/dl, $p<0.05$ in the donation group, and 15.5 g/dl to 14.7 g/dl, $p<0.05$ in the control group. There were no significant between-group differences on either baseline or donation day, $p>0.05$.

4.3 Paper III

Immediate effects of blood donation on physical and cognitive performance a randomized controlled double-blinded trial

Group characteristics

Baseline characteristics were similar between the intervention and the control group.

Maximal oxygen consumption

In the intervention group, we found a significant decrease in $_{REL}VO_{2MAX}$ 41.35 ± 1.7 ml/kg/min on baseline day to $_{REL}VO_{2MAX}$ 39.0 ± 1.6 ml/kg/min on donation day, a 6% reduction, $p<0.05$, and a subsequent significant increase to $_{REL}VO_{2MAX}$ 40.51 ± 1.5 ml/kg/min one week after donation day. Hence, recovery from baseline test to re-test one week after donation. There was no difference in $_{REL}VO_{2MAX}$ between groups on any test day, $p>0.05$.

The intervention group showed a significantly increased heart rate at submaximal performance on donation day compared to the control group, $p<0.05$. In contrast, the maximal heart rate did not change, $p>0.05$.

Hemoglobin concentration

[Hb] was measured before and after testing on each test day. Pre-testing [Hb] in the donation group at 15.8 g/dl significantly decreased on Donation day to 15.1 g/dl, $p<0.05$, and on Day 7 to 14.6 g/dl, compared to donation day, $p<0.05$. In the control group, we found 15.4 g/dl at baseline, 15.2 g/dl on donation day, and 15.2 g/dl on day 7. The reduction from baseline to donation day was significant, with $p<0.05$. There was no difference between donation day and day 7, $p>0.05$. There were no significant differences between the groups on any test day regarding the post-testing [Hb], $p>0.05$.

Capillary lactate

Between-group analysis of capillary lactate showed no difference on any test day. One week after donation day, lactate concentration was significantly increased at 0 minutes (11.9 ± 0.5 mmol/L vs. 10.9 ± 0.4 mmol/L, $p = 0.015$) and 10 minutes (11.6 ± 0.7 mmol/L vs. 10.7 ± 0.5 mmol/L, $p = 0.04$) in the donation group.

Hopkins verbal learning test

The total score did not show any significant difference between the groups on test days or within-group differences on test days, $p>0.05$. Delayed memory showed a significant improvement in the control group from baseline at 9.5 ± 0.3 to 9.7 ± 0.3 on donation day and a subsequent significant decrease to 9.1 ± 0.4 one week later, $p<0.05$. There were no between-group differences on any day, and the donation groups delayed scores remained unchanged through all tests, $p>0.05$.

Trail-making test

Both groups improved their results from baseline to donation day and one week later. The donation group improved significantly from 65.7 seconds at baseline to 52.3

seconds on donation day, $p=0.003$, and further not significantly to 51.3 seconds on day 7, $p>0.05$. The control group also improved from 55.6 seconds at baseline to 50.9 seconds on donation day, $p>0.05$, and to 43.9 seconds on day 7, $p<0.05$. There were no significant differences between the test groups on any test day, $p>0.05$.

Stroop test

Both groups improved their performance on each test day. The intervention group improved significantly from 54.4 seconds to 48.3 seconds to 44.2 seconds on each test day, $p<0.05$. The control group improved on all three test days, from 48.5 seconds to 46.4 seconds to 41.7 seconds. This improvement was only significant between donation day and day 7, $p<0.05$. There were no significant differences between the two groups on any test day, $p>0.05$.

5. Discussion

This dissertation investigates donor safety aspects in walking blood banks due to concerns about donor performance immediately after blood donation in settings where the donor needs to return to strenuous activities as soon as the donation is completed. The concern was raised when NORNAVSOC evaluated the walking blood bank concept in a far-forward setting. As civilian preparedness plans now include walking blood banks, the concern is equally relevant for this service. We hypothesized that donating 450mL of whole blood does not significantly affect physical or cognitive performance immediately after donation. The hypothesis and four specific aims were investigated through three clinical trials. Before evaluating the results, the methods chosen to explore this knowledge gap must be discussed.

5.1 Methodological considerations

The overall concept of investigating donor safety in a walking blood bank setting was to compare baseline performance with performance within 30 minutes of donation. Paper I and II were executed with SOF personnel, and Paper III with regular blood donors. Previously the effects of blood donation have been investigated within 1-24 hours after blood donation, seldom with a shorter timeframe. Therefore, testing time points in this thesis should be adequate. Since this project was initiated in 2011, the topic has been enlightened with at least five more papers, only three of them with a short timeframe (two hours) from donation to re-testing. Papers II and III had a control group undergoing sham donation, a measure last documented in a research setting by Howell in 1964 (100) and repeated by Nadler et al. in 2020 (22).

Paper I was planned and executed while NORNAVSOC implemented a walking blood bank concept designed to answer Aims 1 and 4. Studying the effects of a donation seemed imperative for further development, and there were significant concerns about whether blood donations would significantly reduce the capabilities of SOF soldiers.

The investigators knew they were most likely biased toward a positive result. Equally, the candidates were also biased toward wanting a positive result hence this would provide blood availability for themselves when going to war. Considering these aspects, we conducted the trials objectively, seeking help and advice from colleagues and hiring professionals for the $VO2_{MAX}$ testing.

Paper I does not have a control group, the number of candidates is small, randomization was done by availability, and parts of the study were not designed for statistical analysis. The lack of a control group makes it uncertain whether a variation from test day to test day is due to the blood donation and reduces validity. A small study further weakens the internal and external validity of the study. The homogeneity of the group further reduces the translation of findings to the general population. Proper randomization could have strengthened the study by increasing internal validity.

Special forces soldiers have a tight schedule, so to be able to conduct the trial, we decided to adapt to their schedule and conduct the trials based on availability, knowing this could result in selection bias. At the possible time frame for the trial, there were no available test labs for the direct measure of VO_{2MAX}. Through a standardized protocol, VO_{2MAX} was estimated, and this method is more inaccurate than the direct measure, which reduces the reliability and validity of the result.

Paper I included two soldier-specific skills, hiking with a backpack and a shooting test, tests which increase internal validity.

The cognitive functions were studied by a shooting test that required total concentration and awards responsiveness and inhibition. It could be argued that conventional cognitive testing could have been performed. Still, the shooting test was the most apparent test to evaluate the possible immediate effects of a blood donation. Thus, the first study may be regarded as a feasibility study. Timed hiking with a backpack was not designed for statistical analysis; hence, these results only indicate feasibility.

Paper I also investigated whether non-medics could learn field donation and transfusion procedures to alleviate the medic's work in a casualty situation. These results are not translatable to a general population, hence the group's homogeneity.

Paper II had a small sample size, a homogenous group of special forces soldiers, implying the same concerns as in Paper I. The trial was designed to answer Aim 2, and we did only minimal hematological sampling and no cognitive testing. The main objective of Paper II was to examine physical performance immediately after blood donation when soldiers were fatigued. We did not include cognitive testing in Paper II as this was practically impossible given the location and state of exhaustion the soldiers experienced.

The same selection and motivational bias were present in Paper II as in Paper I. A measure to reduce this was using a control group and blinding the blood donation from the subject and the VO_{2MAX} test operator.

In Paper III, the main objectives were to investigate physical and cognitive performance in a group of regular blood donors and were designed to answer Aim 3. This study's external validity is higher than papers I and II. The study is also prospective, randomized, and double-blinded, increasing external validity. Even though regular blood donors are a heterogenous group, it is still a selected group, so selection bias is present. Our test parameters for physical and cognitive measures are well-known and frequently used in performance testing. Still, it is unknown to the author that the battery of tests used in Paper III has been applied in a similar study. Therefore, the external validity of the results is uncertain, and the study can still be appreciated as a pilot study.

All three Papers are prospective, controlled trials; the primary intervention is the same, and the time from intervention to re-testing is short. The primary outcome in all three Papers is VO_{2MAX}. The variation lies in the pre-condition and heterogeneity of the populations. Two out of three papers included cognitive testing, and these conditions give the project validity and reliability.

Hematological testing

We did not perform any iron storage analysis in any of the trials. This is a possible confounder since iron deficiency is associated with reduced cognitive and physical performance (79). However, this concern is not as important for one-time donations.

Ethics

Ethical aspects of these trials include the risk of the common side effects with blood donations: vasovagal episodes, bruising, and infection after penetrating the skin, with vasovagal reactions being the most severe (55). SHOT reports that these side-effects occur in 2-5% of donations (55) in Great Britain, and Norwegian data from TROLL reports 0.13% (63). A Spanish trial of about 68000 voluntary blood donors found an incidence rate of 0.15% (122). Hence, the risk of these complications is low, and the consequences for the donor are manageable, so the possible burden for the volunteer is considered acceptable.

Walking blood banks in rural areas and small populations raise several ethical aspects. The Blood Care Foundation highlights an increased risk of transmitting infections when lacking screening capabilities and significant social complications if a donor is rejected due to risk-related behavior (94). One can also argue whether donors are volunteers or if they experience peer pressure in a small community.

From the patient's perspective, mortality from trauma is high and further increased in rural areas (123) and could be even more needed here. The practitioner on site must weigh all these considerations against each other when deciding whether to activate a walking blood bank.

Walking blood banks exist and are currently an appreciated solution to preparedness plans internationally (98). Therefore, we argue that it is unethical to not inform donors of the possible risks of donating blood in a walking donor setting, and these trials were warranted.

Another ethical concern is the use of soldiers in medical studies. Due to the strictly defined commander/soldier relationships in the military forces, it may be anticipated that it would be difficult for a soldier to refrain from participation in an activity supported by an officer. In preparation for the studies, the soldiers were extensively informed about the studies, their consequences, and their risks. As indicated earlier, the attitude of the soldiers was influenced by the fact that they considered the availability of a walking blood bank as a major advantage for their safety. We did consider other possibilities but could not find any group that could "mock" the special soldier group.

5.2 Discussion of the results

Through the papers in this dissertation, we have explored donor performance immediately after blood donation in active-duty SOF soldiers and regular blood donors. We found that a regular blood donation did not significantly affect physical or cognitive performance immediately after donation. Paper I addresses the question in well-rested SOF soldiers and identifies no difference in physical performance or combat readiness skills immediately after donation, addressing Aims 1 and 4. In Paper II, physical performance was reduced by about 7% after blood donation in fatigued SOF soldiers, addressing Aim 2. Paper III investigated the effect on cognitive and physical performance immediately after blood donation in regular blood donors and found a 6% reduction of aerobic capacity while cognitive performance was maintained, addressing Aim 3.

Reduced VO_{2MAX} immediately after blood donation has been found by others both historically by Kaepovich in 1942 (99) and Markiewicz in 1981 (104), and most recently by Carius et al. in 2021 (111), Nadler et al. in 2020 (22), Stangerup et al. In 2017 (110), Hill et. Al. in 2013 (108), Judd et al. in 2011 (106), and Gordon et al. in 2010 (105). It is also the conclusion of two recent reviews (113, 114). There are only a few trials that contradict this. Howell and colleagues did a trial in 1964 examining physical capacity immediately after blood donation. What's unique about Howell´s study is that they made a sham donation, and their design left all candidates believing

they had donated blood. Interestingly, they found reduced work capacity immediately after donation in both groups (100). The authors explained their findings with motivational aspects with the donor, hence participant bias or a placebo effect. Nadler et al. again designed a blinded study with a sham donation in 2020. They investigated soldier-specific skills and cognitive performance in a non-inferiority design, and did not find that performance was reduced compared to no-donation (22), similar to Paper I. Nadler et al., investigated anaerobic capacity and therefore, their findings on physical performance cannot be compared to what Howell or we have reported. Interestingly, these three papers with a control group and a blinded donation did not find differences between donation and control groups. There several possible explanations to this.

The placebo, or nocebo, effect explain how verbal conditioning and cues from expectations can affect performance (124), and this ca be linked with the groups' characteristics being highly motivated and selected from the general population in our Paper I. All three studies are also underpowered and consist of heterogeneous groups. Hence the results can be coincidental and are not externally valid.

The general public probably assumes that physical performance is reduced after blood donation, as Calbet highlights in his Editorial for Transfusion in 2017 (125). These contradictory results underline the importance of valid study designs when investigating donor performance after blood donation.

Reduced maximal oxygen consumption

In Papers II and III, we found reduced VO_{2MAX} on donation day compared to baseline testing. In the blinded control groups, the reduction was not present. This strengthens the finding, especially the between-group difference enforces that the independent variable (the blood donation) caused an effect. This is also as expected physiologically and what is accepted internationally in two recent reviews (113, 114). Others have investigated the optic throughout history, like Balke et al. in 1954, where they found significantly reduced work capacity within one hour of a 500mL blood

donation in a group of 14 candidates (116). And more recently, Ziegler in 2015 (109) and Stangerup in 2017 (110).

Physiologically one would expect a decreased oxygen delivery capacity after donating 450mL of blood. First, the circulatory volume is decreased, reducing cardiac output according to Fick's principle (69). Secondly, the reduction in hemoglobin after blood donation constitutes about 7-10% of the oxygen-carrying capacity (101). The volume depletion of a blood donation is compensated by the immediate effects of the sympathetic nervous system augmented by the neuroendocrine system (69), fluid shifts to the vascular bed according to the Starling forces (70, 72), and after a while, the RAAS and increased EPO initiated by the kidneys (69).

Compensating reduced blood volume

Elevated heart rate during submaximal performance after blood donation, as found in Papers II and III and confirmed by others (105, 107), is a compensatory mechanism for the reduced oxygen-carrying capacity. On corresponding levels of physical activity, oxygen demand from the tissues should be equal. Thus increased heart rate expresses a compensation mechanism for the reduced blood volume and oxygen-carrying capacity, according to Fick's principle (69), and supports the physiological rationale. Increased heart rate increases cardiac output to compensate. In Howell's study in 1964, they found similar results, which were even more apparent when they used oxygen pulse as the measure. Oxygen pulse is oxygen consumption divided by heart rate. When oxygen-carrying capacity is reduced, more heartbeats are needed to transport the same amount of oxygen to the tissues as long as the workload is static (100). Others have also found that submaximal heart rate increases after blood donation, most recently by Carius et al. (111). We did not find an increased maximal heart rate, in line with other publications (103, 106). Thus, the maximal sympathetic response is most likely activated at the end of physical testing independent of a blood donation.

In Paper II, hemoglobin concertation was significantly reduced in both groups on donation day is most likely an effect of the strenuous exercise more than the donation

itself. Strenuous physical activity causes auto-hemodilution, and lower blood viscosity increases aerobic fitness (126).

In Paper III, [Hb] were maintained on donation day and reduced one week after donation. It is well known that hemoglobin is reduced after blood donation (70, 75, 109, 110). The lost volume is replaced within hours after the donation, both the plasma volume and the volume of the red blood cells (109). Thus, the red blood cells are only partly replaced one week after blood donation, whereas the volume is completely replaced. Theoretically, the circulatory system may be in a net excess volume state, which increases stroke volume according to Fick's principle and the Frank-Starling effect and positively affects VO_{2MAX} (127). It is also suggested that a reduced blood viscosity improves aerobic capacity and thus normalizes VO_{2MAX} before the oxygen-carrying capacity is normalized (126).

In Paper II, we found somewhat conflicting but indicative results that lactate levels were elevated in the donation group after exercise one week after donation but not on donation day. Lactate is identified as a marker for oxygen debt (128, 129), and these results indicate that the oxygen debt one week after blood donation increased compared to the control group. Similar results were absent on donation day, which remains unexplained because this could be anticipated after the volume depletion and reduced oxygen delivery capacity. A possible explanation could be related to the measurement uncertainty of capillary lactate, and it is well known that reliable measuring of capillary lactate is challenging (21).

Cognitive performance

Cognitive testing in Paper III did not reveal decreased cognitive performance in the donation group. There were some differences between groups on baseline testing, which is common in groups this size. There was a trend in both TMT and the Stroop test in both groups to perform better for each test day. This could reveal a learning effect and weakens the results. The Interval study is currently the best evidence of adverse cognitive effects after blood donation (130). Still, it investigated the long-term effects of blood donation and was not a clinical trial. More than 45.000 blood

donors in England U.K. self-reported adverse reactions to blood donation, including cognitive function: No adverse cognitive effects of blood donation were reported (130). Recently Nadler et al. investigated cognitive performance immediately after blood donation in a group of Israeli soldiers. In the blinded and controlled trial, they did not find decreased cognitive skills in the donation group immediately after donation, corresponding to our results in Paper III. Physical fitness correlates positively with cognitive performance, but whether a sudden decrease in VO_{2MAX} will affect cognitive functions is unclear. Our results suggest that executive functions are maintained immediately after blood donation, despite reduced VO_{2MAX}.

A 100% success rate in the field donation training indicates that non-medics can contribute when buddy transfusion is needed. In small teams, resources are scarce, and sharing the workload from the medic can be crucial. This training model has been continued in NORNAVSOC since this trial with similar results. Currently, an equal training regimen is incorporated in Finnmarkspiloten, where cross-training between different healthcare professions is emphasized to share the workload in emergent situations (97).

Are the immediate effects of blood donation of significant importance?

We have found decreased VO_{2MAX}, maintained cognitive performance, and shown that blood donors can perform a strenuous physical test immediately after blood donation. The relevance of a 6-7% reduced VO_{2MAX} varies from situation to situation. It may be detrimental in combat or a crisis scenario but mitigated by proactive donor care management.

6. Conclusion and implications

6.1 Conclusion

A standard blood donation causes a decrease in exercise physiology, does not affect cognitive physiology, and maintains performance. Therefore, walking blood banks are feasible and provide resilience. However, some of the risks involved should be acknowledged.

6.2 Implications for clinical practice

Walking blood banks is a safe and effective way of making whole blood available far forward where conventional blood supplies are out of reach, and a scalable preparedness plan for a sudden increase in demand for whole blood. Implications for the donor are minor. The most considerable risk for the donor is probably related to the possibility of becoming a patient shortly after a donation. This raises ethical questions for the provider on the scene about imposing that risk on the donor. With our results, post-donation guidance can be more precise and informs the provider's decision.

6.3 Implications for further research and future perspectives

Further research on post-donation performance is warranted, especially under altered environmental situations like high altitudes, arctic climates, or extreme heat. The extended use of walking blood banks, both as part of preparedness plans in remote areas and to ensure whole blood supplies in larger hospitals, underpins the importance of further investigating the topic. A standardized approach to donor performance evaluation would be an advantage.

Known blood donation side effects such as syncope warrant further investigation when blood banking is moved to the pre-hospital arena. If we accept the risk of donating one unit of whole blood from walking donors, the idea of possible donating more than one unit from each donor rises. That would require more investigation.

All blood donations should be subject to hemovigilance systems. However, should general hemovigilance systems be modified to accept data from walking blood banks, or should there be a separate reporting system?

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Donor performance of combat readiness skills of special forces soldiers are maintained immediately after whole blood donation

A study to support the development of a prehospital fresh whole blood transfusion program

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BACKGROUND: Bleeding is a major cause of death in combat settings, and combat casualties in shock may benefit from fresh whole blood (FWB) transfusion. "Buddy transfusion" is a well-known lifesaving intervention, but little is known about donor combat safety aspects immediately after blood donation. The objectives of this study were to explore the effects of donation of 1 unit of blood on physical and combat-related performance among active duty soldiers. We also investigated the feasibility of a short training program to teach nonmedics buddy transfusion.

STUDY DESIGN AND METHODS: Twenty-five fit male soldiers from a special forces unit were divided into three groups and tested on 1) a Bruce protocol treadmill stress test, push-ups, and pull-ups; 2) a 50-round rapid pistol shooting test; and 3) an uphill hiking exercise carrying a 20-kg backpack. After baseline testing, the soldiers performed the tests again (2-6 min) after donating 450 mL of blood. The training program included blood collection and reinfusion procedures and we measured success rate of venipuncture, time for blood collection, and success in placing sternal intraosseous needle and reinfusing 1 unit of autologous blood.

RESULTS: We did not find any significant decrease in performance either in physical or in shooting performance after donating blood. Nonmedic soldiers had a 100% success rate in blood collection and also infusion on fellow soldiers after a short introduction to the procedures.

CONCLUSION: This study supports the fact that buddy transfusion may be feasible for healthy well-trained soldiers and does not decrease donor combat performance under ideal circumstances.

The Tactical Combat Casualty Care guidelines for fluid resuscitation of soldiers in hemorrhagic shock recommend the use of 500 mL of hetastarch (repeated once, maximum 1000 mL) when altered mental status and/or weak or absent peripheral pulses are present.[1] The most seriously injured are coagulopathic a short time after injury.[2-4] Prehospital infusion of crystalloids or colloids as a replacement for severe blood loss is not sufficiently proven to be a lifesaving intervention.[5-7] New guidelines for damage control resuscitation (DCR) recommend starting early with blood components with red blood cells : plasma : platelets in a 1:1:1 unit ratio to approximate whole blood and to minimize the use of crystalloid.[8] These new clinical guidelines for DCR are designed for use at surgical facilities. Even in the far forward environment (before or during transport) there is a need for addressing the early coagulopathy of trauma and to implement far-forward DCR.[9] The goal of

ABBREVIATIONS: DCR = damage control resuscitation; FWB = fresh whole blood; HRmax = maximum heart rate.

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this prehospital approach is to decrease death from hemorrhage by limiting the development of shock and coagulopathy. An additional benefit of earlier treatment of shock and coagulopathy may also be a reduced requirement for blood components over time.[10]

Blood components are normally not available in the far-forward environment. Each prescreened and typed soldier on the battlefield represents a useful source of whole blood. In situations with delayed transport or long evacuation times whole blood infusion is a potentially lifesaving/life-prolonging intervention. Fresh whole blood (FWB) can be donated by a combat buddy and transfused to the casualty—hence the term "buddy transfusion." Casualties in shock will benefit from a resuscitation fluid that is warm, with maximal oxygen-carrying capacity and hemostatic function.[9] For patients with life-threatening hemorrhagic shock, this is an old and well-proven lifesaving intervention.[11] Recent data also indicate that warm FWB is associated or closely associated with improved 24-hour survival upon adjusted analyses for patients with combat-related traumatic injuries.[12,13]

The authors are in the process of developing a prehospital FWB transfusion clinical protocol that uses healthy soldiers as donors for casualties in life-threatening hemorrhagic shock. We were not able to find consistent data regarding safety for donors who were elite military personnel and in particular how combat readiness skills are affected immediately after donating blood.

The objective of this study was to explore the effects of donation of 1 unit of blood (450 mL) on physical performance and shooting skills among fit active duty elite soldiers. We also tested if the soldiers were able to learn the practical skills (phlebotomy and sternal reinfusion) needed to perform buddy transfusion after only a short lecture on the procedure. This donor safety study is one component of a larger prehospital FWB transfusion research program.

MATERIALS AND METHODS

The study was approved by the research ethics committee of the Regional West Health Trust, Norway. Twenty-five nonsmoking male soldiers, median age 29 years, from a Navy special forces unit consented to participate. Mean body mass index was 24.7 kg/m^2 (range, 22.6-28.3 kg/m^2). This is a pilot study and we were not able to find data in the literature providing information for power calculations regarding the testing we included in the study. The participants were divided in three different groups for testing. The grouping was based on availability at the given time points, and there was no selection to any specific group: Group 1—Bruce protocol treadmill stress test, push-ups, and pull-ups (n = 7); Group 2—50-round pistol shooting test (n = 12); and Group 3—uphill hiking exercise carrying a 20-kg backpack (n = 6). Each group was tested twice, before and immediately after donation of 450 mL of blood.

The soldiers were allowed to rehydrate during the donation procedure and they were all offered a 0.5-L water bottle. The exact volume each participant consumed was not recorded. All 25 soldiers participated in a 60-minute training program aimed at testing whether it is possible to teach nonmedic soldiers buddy transfusion during a short period.

Multistage treadmill stress test, push-ups, and pull-ups

VO_2 max was estimated in seven soldiers. Bruce protocol was followed, using a multistaged treadmill test. Each stage lasted for 3 minutes, and in total seven stages were included in the procedure. For each stage, belt velocity and slope were increased (see Table 1). The soldiers ran until exhaustion (unable to continue running). Heart rate and lactate were measured at the end of each stage and at exhaustion when total time on belt (T) was noted. Lactate was measured in a blood sample from the ear lobule and a portable lactate analyzer (Lactate Scout, EKF Diagnostics, Barleben, Germany) was used. From the total run time used, VO_2 max was estimated as follows:[14] $VO_2\ max = 14.8\text{-}(1.379 \times T) + (0.451 \times T^2) - (0.012 \times T^3)$. The push-ups were performed as "full push-up" in the prone position, with the back and legs straight and off the floor. The hands were placed below each shoulder, with arms fully extended. From this start position, the body was lowered by using the arms until the chest touched the floor, and then back to the start position. Standard pull-ups were performed as a dead-hang pull-up, with an overhand grip. Then the body was pulled up until the chin cleared the bar, and finished by lowering the body until arms and shoulders were fully extended A baseline test (predonation test) was performed 4 days prior to donation, and the postdonation test immediately after donating blood. The soldiers performed the procedures until they were unable to continue. The test endpoint was differences in estimated VO_2 max, maximum heart rate (HRmax), lactate, and number of push-ups and pull-ups.

TABLE 1. Bruce protocol: multistage treadmill test*

Stage	Time (min)	Slope (%)	Speed (km/hr)
1	3	10	2.7
2	6	12	4.0
3	9	14	5.5
4	12	16	6.7
5	15	18	8.0
6	18	20	8.8
7	21	22	9.7

* Each stage lasts 3 minutes, and the slope of the belt and belt speed increases for each stage. (Statistics: Hodges-Lehman estimates of median difference.)

Fifty-round pistol shooting test

Twelve soldiers performed a standard Navy special operational forces protocol rapid shooting test, using their personal weapon (9 mm). The protocol has five separate tests, each with 10 rounds (6 m nondominant hand, 10 m dominant hand, 10 m 2 + 1, 18 m precision, 25 m precision). The predonation test was performed 2 days before donation, and the postdonation test immediately after donating blood. The weather and light conditions were similar on the test days. The study outcome in this exercise was differences in total hits.

Uphill hiking exercise

Six soldiers were tested on an uphill exercise carrying a 20-kg backpack. The track had a 28% slope and 450-m altitude difference; the soldiers were instructed to walk as a group, and no individual time measurements could therefore be recorded. The soldiers walked up and down again as quickly as they were able to (no running) before they donated 1 unit of blood. They then were offered water (ad libitum) to rehydrate without any further break before they repeated the exercise, again walking as quickly as the group managed. The endpoint was the difference in time used by the team on the uphill part of the track. The soldiers also filled in a questionnaire to report possible side effects related to the donation and the postdonation performance.

Buddy transfusion training program

All soldiers (n = 25; all nonmedics) were given a short lecture on marking the blood bag thoroughly with donor identification and blood type and the procedure of starting phlebotomy. Directly thereafter they performed these two procedures on a fellow soldier under supervision of qualified personnel. One participant needed two attempts to get the donation started, all the others managed to start it on the first attempt. Success rate of starting phlebotomy and total time for phlebotomy was measured. A blood banker's electric scale was used to ensure that the right volume was donated. The primary endpoints on this test were phlebotomy success rate and total time for phlebotomy. Reinfusion of autologous whole blood via sternal intraosseous device was also tested in a small group of eight "nonmedics." The soldiers on this procedure were also given a short lecture including a live demonstration of the procedure. The primary endpoint of this test was intraosseous placement success rate and total time of reinfusing 1 unit of blood via sternal intraosseous needle (Fast-one, Pyng Medical Corp., Richmond, British Columbia, Canada).

Data and statistical analysis

The primary endpoint data in Group 1 were evaluated using the Hodges-Lehman estimates of median difference, using computer software (StatXact 7.0, Cytel, Inc., Cambridge, MA). In Group 2 the results were compared using the paired t test, two-tailed test, with level of significance of p values of 0.05. Analysis was performed using a statistical program (SPSS, PASW Statistics 18, SPSS, Inc., Chicago, IL). In Group 3, ordinary statistics were not applicable because they performed the testing as a group, not as individuals, but differences were not considered significant if the group performed better after donating blood. The buddy transfusion data are described, using success rate, mean time, and range. Data are described using the mean ± standard error (SE) and median when appropriate.

RESULTS

We did not find any significant decrease in physical performance after donating 450 mL of blood (Table 2). With the Bruce protocol, there was a small, nonsignificant, decrease in estimated maximal oxygen consumption from 61.3 mL/kg/min before donation to 60.2 mL/kg/min immediately after donation. HRmax was unchanged at 190 beats/min. Maximum lactate levels also show no difference before and after donation. There were also no differences with pull-up and push-up testing. On average the soldiers did one fewer pull-up and one more push-up after donation.

Shooting performance (Table 3) was also unchanged after donation of blood. Hits increased from a mean of 35.3 of 50 to 37.1 of 50. There were no subgroup differences.

In the uphill walk, the group performed 2 minutes better after blood donation (35 min before and 33 min after donation). No adverse effects after blood donation were reported during the second walk.

TABLE 2. Results from multistage treadmill test before and after donation of 450 mL of blood*

Variable	Before donation†	After donation†	λ (95% CI)
Belt time (sec)	994 (62.0)	977 (56.2)	–11.00 (–32.5 to 9.0)
VO_2 max (mL/kg/min)	61.1 (3.7)	60.1 (3.4)	–0.66 (–1.7 to 0.5)
HRmax (beats/min)	190 (2.5)	190 (1.3)	–1.00 (–9.0 to 2.0)
Lactate (mmol/L)	12.9 (8.8)	11.3 (8.5)	–1.58 (–2.5 to 0.8)
Pull-ups	15 (5.9)	14 (4.9)	–1.50 (–7.0 to 2.0)
Push-ups	50 (7.3)	51 (8.2)	–1.25 (–6.0 to 8.0)

* The median difference (λ) and the upper and lower limits of the 95% CI for the median difference are displayed. (Statistics: Hodges-Lehman estimates of median difference.)
† Data are reported as median (SD).

TABLE 3. Fifty-round pistol shooting test with five separate tests (nondominant hand, dominant hand, 2 + 1, and precision): distance from shooter to target in meters, number of rounds per test, and mean (SE) hits per test before and after donation*

Protocol	Distance (m)	Rounds	Hits†		p value
			Before donation	After donation	
Nondominant hand	6	10	7.3 (0.4)	8.3 (0.4)	
Dominant hand	10	10	6.5 (0.5)	6.3 (0.6)	
2 + 1	10	15	12.4 (0.6)	12.8 (0.6)	
Precision 1	18	10	6.3 (0.4)	6.4 (0.7)	
Precision 2	25	5	2.7 (0.4)	3.4 (1)	
Total			35.3 (1)	37.1 (1.7)	0.61 (NS)

* Statistics: paired t test, two-tailed test.
† Data are reported as mean (SE).
NS = not significant.

For soldiers who completed the educational program the success rate of starting phlebotomy was 100%. Only one participant needed two attempts to get the donation started. The median time for phlebotomy was 6 minutes 8 seconds. The success rate of correctly placing the sternal intraosseous needle was 100%. The total time used for reinfusing 1 unit of whole blood via the intraosseous route (gravity only, no external bag pressure) was 19 minutes 30 seconds (range, 8 min 30 sec-30 min 10 sec).

DISCUSSION

The main finding in this study is that donation of 450 mL of blood by a Norwegian Navy special forces soldier does not immediately reduce physical performance or combat skills. It is important to recognize that this study was performed under ideal conditions and might not be comparable to strenuous field conditions. Few studies on donor performance after blood donation are available, and the results are conflicting. Birnbaum and coworkers[15] found that among 10 healthy male subjects with low to moderate physical activities the donation of 1 unit of blood decreased (24 hr after donation) VO_2 max due to a 20.6% decrease in oxygen delivery (DO_2). Reduction in DO_2 was due to reduction in hemoglobin (Hb) and stroke volume. Similar results are reported from Burnley and coworkers.[16] Panebianco and colleagues[17] evaluated 10 male cyclists and found that maximal performance was decreased for at least 1 week with no changes in submaximal performance. Their findings indicated that donation of 1 unit of blood decreased VO_2 max due to the decrease in cardiac output. They found unchanged HRmax but reduced stroke volume. However, they used a different method for calculation of VO_2 max. No previous studies have used military soldiers or elite military personnel as subjects in donor performance studies. It may therefore be true that a blood loss of 450 mL does not reduce VO_2 max in this extremely fit study population, but this observation needs to be confirmed by other studies.

Most studies performed on physical performance and oxygen uptake after blood donation have a time frame of at least 24 hours from blood donation to exercise performance testing. Gordon and coworkers[18] investigated the changes within 24 hours after donation and found that the compensatory mechanisms in fit young people counteracted the loss in Hb mass. The selection of donors in this study is from well-trained special operational forces soldiers with a relatively high muscle bulk mass compared to a normal population and mean blood volume might be higher compared to other study population. One unit of blood therefore represents a relatively lower percentage of the total blood volume and some of the findings might be explained by this fact.

Minutes after donation Hb levels remained unchanged[19] and any changes in DO_2 must have been related to changes in Q. We did not find significant changes in HRmax and treadmill run duration before and after donation. This indicates that stroke volume is maintained immediately after donation in this donor population. What compensatory mechanism this is due to remains unexplained. It might also be that the indirect method used for calculating VO_2 max in this study is inaccurate.

We believe that improvement of far-forward resuscitation of casualties in hemorrhagic shock is needed. If DCR strategies should be put further forward, one of many solutions is to design educational programs to teach selected soldiers practical skills needed to perform buddy transfusion. Also, further studies to clarify the effects of donations on the soldiers as well as efforts to optimize the blood components are necessary.

Limitations of the study

This is a pilot study with a limited number of highly fit participants. The purpose of the study was to get an impression of what the effects of a 450-mL blood donation would be. Based on our findings, it will be possible to design larger studies, as we now have some data that may

be the basis of power calculations. Due to the fitness of the participants, the results may not be true for other groups, as the regular blood donor corps. At the time of testing, our participants were in normal conditions, which certainly may not be representative for the conditions after weeks or months in the battlefield. We therefore want to repeat the study after the soldiers have been through hard and enduring mental and physical stress.

As the soldiers were highly motivated, and during the training on blood transfusions learned this procedure, the findings should not be generalized. As "buddy transfusion" is important in extreme settings, studies involving randomization and blinding of the study subjects are warranted.

In conclusion, our results indicate that physical and combat performances after whole blood donation are preserved within acceptable limits for healthy well-trained elite soldiers. We have also shown that soldiers are able to learn the practical skills (phlebotomy and sternal reinfusion) needed to perform buddy transfusion after only a short lecture on the procedure. The study supports further development of a prehospital FWB transfusion program.

CONFLICT OF INTEREST

The authors have no conflict of interest in connection with this manuscript.

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Making whole blood available in austere medical environments: donor performance and safety

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BACKGROUND: To provide whole blood on the battlefield can be a challenge, but a buddy system protocol is both an elegant and the only currently available means to supply blood to a Special Forces team in far-forward locations. Our aim was to investigate donor-safety associated with such a protocol.

METHODS: This study was a randomized, double-blinded, controlled trial that aimed to evaluate the immediate effects of a 450 cc blood donation on physical performance in fatigued and dehydrated Special Forces soldiers. The primary outcome variables were absolute and relative maximal oxygen uptake (VO_{2max}), exercise tolerance time (ETT) and heart rate (HR).

RESULTS: Relative VO_{2max} decreased by 7.1% in the donation group between pre and posttest, compared to no change in the control group. Absolute VO_{2max} decreased by 11.2 and 3.6% between pre and posttest in the donation and control groups, respectively. Mean ETT in the donation group was on average 92 seconds shorter compared to baseline, which represents a decrease of 9.5%.

CONCLUSION: Donating blood after a week of strenuous physical activity is feasible for Special Forces personnel. While the donation results in some diminishment of VO_{2max}, a 3.6%-11.2% decrease in relative VO_{2max}, and in elevation of submaximal HR levels highly trained personnel continue to perform well both at both sub-maximal and maximal effort levels.

INTRODUCTION

Knowledge gained by medical practitioners in military conflicts over the last decade has contributed to significant changes in transfusion strategies addressing traumatic hemorrhagic shock.[1] The transition from a crystalloid and/or colloid-based resuscitation approach to one that is blood-based is reflected in the fluid preferences for resuscitation of hemorrhagic shock recommended in the recent Tactical Combat Casualty Care (TCCC) guidelines. TCCC guidelines now recommend that whole blood (WB) be used as the primary resuscitation fluid.[2] This is also a current trend in the civilian EMS services in several countries.[3] And an increasing number of NATO and other allied nations are implementing TCCC guidelines in recognition of the published improvements in the survival of severely injured combat wounded over the course of the decade-long conflict. The guidelines have undergone continuous

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reevaluation, resulting in optimized treatment strategies that are associated with lower mortality and morbidity of wounded service personnel.[4]

Before the TCCC guidelines were changed in 2014,[2] some military units had already revised their protocols in favor of WB-based resuscitation strategies. The U.S. 75th Ranger Regiment and the Norwegian Naval Special Operations Commando (NORNAVSOC) have implemented protocols that now include the use of freeze-dried plasma, cold-stored whole blood, and warm fresh whole blood (WFWB). Successful WFWB implementation relies on the establishment of the so-called "buddy transfusion" system, in which military personnel are paired by compatible blood types so that donors are available for each other in the smallest of service units. It is based on a far-forward "walking blood bank" concept in which service personnel at the scene of action donate blood for immediate transfusion of a severely bleeding casualty. A buddy system protocol is not only an elegant way of providing an optimal, equal ratio blood product without the functional loss and logistical challenges associated with blood storage, it is the only currently available means to supply blood to military units operating in far-forward locations. We believe this could be equally valid in civilian settings like small, geographically remote communities, or even in cruise liners operating far away from medical treatment facilities. As an example, Royal Caribbean Cruiseliners (RCCL) has successfully implemented a "buddy transfusion" protocol on board their 32 cruise liners with excellent results. Some questions remain unanswered; however, such as whether the known reduction in exercise performance immediately after donation of 450 mL of blood causes significant impairment, and whether civilian proscriptions against post-donation exercise can be disregarded. The blood bank at Haukeland University Hospital in Bergen blood donors are instructed to avoid rigorous physical activity for 24 hours after donation of a unit of blood.

Execution of blood donation in military settings is not only a medical decision, but also a tactical one, and the potential for a "walking blood bank" to put the rest of the team in harms' way must be fully evaluated. A literature search was conducted, and while several reports of change in exercise performance 24 hours post-donation were found these studies were insufficient to fully address the impact on overall performance.[5-12]

Physical performance after blood donation is poorly described in the literature before this study, and the effect of the extreme conditions encountered in a Special Forces field exercise on donor performance have not previously been evaluated. The main difference from other trials is the extent of preconditioning our subjects underwent before blood donation and retesting. In 2012 we postulated that donation would not have immediate post-donation effects, and to test the hypothesis we conducted an exercise performance evaluation on physically fit members of a Special Forces unit and found that donor performance was not adversely affected immediately after donation of a full unit (450 mL).[13] This study was performed on rested service personnel under optimal conditions, however, which is unlikely to simulate realistic field conditions. During an actual mission, donors are likely to be suffering from fatigue, hunger, and dehydration, which could adversely affect the donor's ability to maintain optimal performance after donation. A thorough literature search did not uncover relevant publications on this subject, and thus a follow-up study was designed to address this question. Such a study is necessary to adequately test whether "buddy transfusion" protocols can be implemented without incurring unacceptable risks to the donor. A far-forward WFWB resuscitation protocol in an austere environment with possible prolonged evacuation times is potentially life-saving.

Combat readiness skills are difficult to measure, and universally adopted, validated metrics to assess performance have not been established. In our previous study, we focused on two skills which are indispensable on most field missions and tested them independently; these were maximal oxygen consumption (VO_{2max}) and hiking as a measure of endurance and shooting skills as a measure of cognitive performance. Prioritizing these skills would be difficult in a deployed environment, but given that endurance is a precondition of cognitive metrics of performance, this study focused on VO_{2max} assessment. We hypothesized that a 450 mL blood donation does not affect VO_{2max} performance under conditions of severe fatigue.

MATERIALS AND METHODS

This study was a randomized, double-blinded, controlled trial that aimed to evaluate the immediate effects of a 450 mL blood donation on physical performance in fatigued and dehydrated subjects, approved by The Regional Ethics Committee in Bergen – Norway. The primary outcome variables were absolute and relative maximal oxygen uptake (VO_{2max}), exercise tolerance time (ETT) and heart rate (HR). Direct measurement of VO_{2max} was selected as a marker of endurance capacity since it is often considered the "gold standard" method for determination of aerobic fitness.[14] ETT is a validated measure of physical performance.[15] Similarly, submaximal HR correlates with performance capacity,[16] and results were compared to those of the control population.

Subjects and sampling

All NORNAVSOC soldiers participating in the 2013 spring exercise "Quick Feet" were invited to participate in this study (n = 13), all of who were male. No females were

available for invitation. Successful completion of the exercise was the inclusion criterion, and pre-exercise data collected from excluded subjects were not included in the final analysis. All participants provided written consent after full disclosure of risks and benefits were presented in both oral and written form. As expected, not all participants were able to finish the exercise, one due to arthritis and one due to general illness, and thus were excluded from the final analysis. After randomization, the study groups consisted of six donors and five controls.

The mission consisted of a 6-day field exercise in which subjects endured 16-18 hours/day of marching through rough terrain carrying all necessary supplies in a backpack weighing 16-18 kg. The exercise simulates conditions in which participants are caught behind enemy lines and must evade capture while traveling to safety. Randomization using the coin flip technique was performed after completion of exercise. Power analysis was not possible to perform due to lack of similar work done in the past.

Measurements

All required personnel and equipment to perform the study, including a deployable test-lab for VO_{2max} testing, was forwarded to the Naval Special Forces facility in northern Norway. Pre-exercise testing and post-exercise and blood donation testing was performed according to the same protocol, under standardized conditions, and test technicians remained unchanged.

During exercise preparations at the base all candidates underwent baseline testing one day before they were deployed. Candidates returned to the base via helicopter at the end of the exercise and reported for retesting within 20 minutes of arrival. Blood samples (10 mL total) were collected in glass tubes (Vacuette EDTA and GEL) before blood donation and VO_{2max} testing. The GEL glass tubes underwent centrifugation within 30-120 minutes after blood withdrawal, at 3000 rpm for 10 minutes and then stored at room temperature for 6 hours. The EDTA glass tubes were stored at room temperature for 6 hours. Room temperature storage and centrifugation was done at the test site before blood samples were sent to the University Hospital of Northern Norway – Harstad for analysis, a 1-hour drive away. Body weight was measured using a calibrated, digital scale, and stadiometer (model 708; Seca Corp. Hamburg, Germany) to the nearest 0.1 kg and 0.5 cm, respectively. Subjects wore light sport clothing and removed their shoes before being weighed. Before analysis, 0.2-0.5 kg was subtracted from the weight to adjust for clothing weight.

All candidates underwent venipuncture of the middle antecubital vein with a 14-gauge needle (Terumo BCT, Lakewood, CO) regardless of study assignment, and received blacked-out goggles and Peltor Optime II Earmuffs to prevent them from discovering whether a unit of blood was being taken or not. Blood units were collected in standard CPDA-containing blood bags (Terumo BCT, Lakewood, CO) and a blood collection mixer scale (Baxter, Deerfield, IL) was programmed to collect 450 mL of blood, following current standards for blood collection in Norwegian blood banks. For subjects in the control arm, the collection bag tubing was occluded to prevent blood collection. Investigators involved in data analysis were blinded to donation allocation by physically separating the VO_{2max} test laboratory from the blood donation site.

VO_{2max} was measured according to the manufacturer's instructions through a three-way directional valve (model 2700, Hans Rudolf Inc, Kansas City, MO) according to the Bruce Protocol in the mobile test laboratory, starting at 2.7 km/hour and 10% inclination.[17] The test was performed on a treadmill (PPS 55 Sport, Woodway GmbH, Weil am Rhein, Germany) using an automatic predefined stepwise protocol with increasing speed and incline. The treadmill was calibrated on elevation and speed before both tests. The subjects ran until exhaustion, and ETT to the nearest second was registered. HR was monitored in all subjects during the test (S610, Polar Electro OY, Kempele, Finland) and the highest HR attained was defined as peak heart rate (HR-peak). Oxygen uptake was measured continuously with an automatic metabolic system (Oxygon Pro, Erich Jaeger GmbH, Hoechberg, Germany) using the mixing chamber mode setting at 30-second sampling intervals. This system has been verified to be accurate for measuring oxygen uptake.[17] Testing was performed in a temperature-controlled environment (17°C-20°C) with adequate ventilation. The online system was gas-calibrated with room air and certified calibration gases, and volume was calibrated manually with a 3 L syringe (Hans Rudolf Inc., Kansas City, MI) before every second test. The mean of the two highest consecutive measurements was defined as VO_{2max}. The determination of whether maximal effort had been reached during the VO_{2max} test was a subjective assessment made by the test technician. In cases when there was doubt as to whether $VO_{2max}$was reached, the test was accepted if peak respiratory exchange ratio was above or equal to 1.05.

Statistics

The normal distribution of primary outcome variables was assessed with the Shapiro-Wilk test and visual inspection. Differences within groups (pre to posttest) were analyzed with a paired-sample t test, and an unpaired t tests was used to check for differences between groups (BD vs. CON group). Data are shown as mean values, including 95% confidence intervals (CI) or 1 standard deviation (SD). Statistical analyses were performed in SPSS (version 21, IBM Corp., Armonk, NY). A p-value <0.05 was considered statistically significant.

TABLE 1. •••

	BD (n = 6)			CONT (n = 5)		
	Pre	Post	Change	Pre	Post	Change
BW (kg)	87.7 (83.7, 91.7)	83.9 (80.1, 87.6)	−3.8 (−4.7, −3.0)*	87.5 (68.5, 106.5)	84.6 (66.8, 102.4)	−2.9 (−4.5, −1.3)*
ETT (sec)	968 (933, 1002)	876 (813, 939)	−92 (−144, −40)*	970 (921, 1019)	937 (849, 1025)	−33 (−80, 14)
VO_{2max} (L/min)	4.91 (4.59, 5.23)	4.36 (3.98, 4.73)	−0.55 (−0.70, −0.41)*†	5.03 (4.22, 5.84)	4.85 (4.18, 5.51)	−0.18 (−0.45, 0.08)
VO_{2max} (mL/kg/min)	56.0 (52.9, 59.2)	52.0 (48.4, 55.6)	−4.0 (−5.6, −2.5)*†	57.8 (53.4, 62.3)	57.8 (51.3, 64.4)	0 (−2.8, 2.8)
RER	1.19 (1.17, 1.21)	1.13 (1.09, 1.17)	−0.06 (−0.10, −0.02)*	1.19 (1.15, 1.23)	1.13 (1.09, 1.18)	−0.06 (−0.12, 0)
Ventilation (L/min)	177 (164, 191)	162 (150, 174)	−15 (−39, 8)	175 (150, 201)	168 (149, 186)	−8 (−23, 8)

NB. p = 0.06 for difference in change in ETT between BD and CONT group.
* $p < 0.05$ between pre and posttest within group.
† $p < 0.05$ between BD and CONT group.
BW = body weight; BF = body fat; ETT = exercise tolerance time; VO_{2max} = maximaloxygenuptake; RER = respiratory exchange ratio.

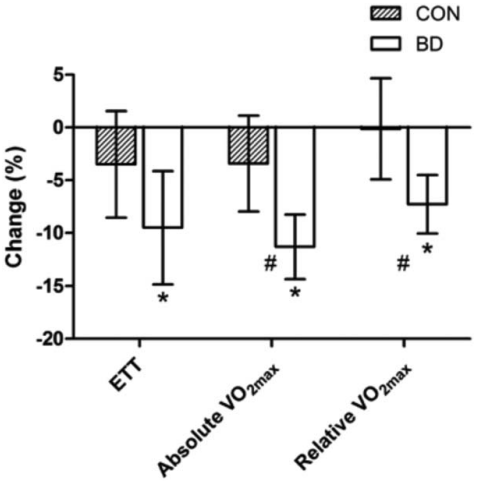

Fig. 1. Figure shows percentage difference in exercise tolerance timen (ETT), relative and absolute oxygen uptake between the control group (CON) and the donation group (BD), and inbetween the same group. * indicates $p < 0.05$ between pre and posttest within group. # indicates $p < 0.05$ between BD and CONT group.

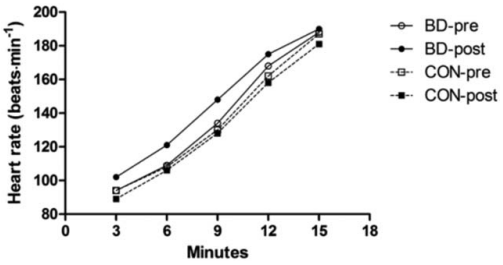

Fig. 2. Figure shows mean submaximal HR (y-axis) level at the end of each level of the Bruce protocol (x-axis). The four groups are: BD pre – Donation group pre-exercise, BD post – Donation group post-exercise, CON pre – Donation group pre-exercise, CON post – Donation group post-exercise.

RESULTS

There were no significant differences in age or weight between the two groups. Mean bodyweight in the test and control groups varied before and after the exercise, but not between groups (loss of 3.8 and 2.9 kg, respectively; Table 1).

The Shapiro-Wilk test confirmed that primary outcome variables (VO_{2max}, ETT, and HR) were normally distributed. Relative VO_{2max} calculations showed a 7.1% decrease in mean VO_{2max} in the donation group between Test 1 and Test 2 (Fig. 1), compared to no change in the control group. Absolute VO_{2max} decreased by 11.2 and 3.6% between pre and posttest in the donation and control groups, respectively (Fig. 1). Differences were statistically significant in both cases.

Mean ETT in the donation group was on average 92 seconds shorter compared to baseline, which represents a decrease of 9.5% (Fig. 1). Yet, this change did not reach significant level (p = 0.06).

Figure 2 shows mean submaximal HR level at the end of each level of the Bruce protocol. Donor HR increased significantly compared to baseline at all submaximal levels. Control group HR did not differ at submaximal performance levels post-exercise.

Hemoglobin

Mean Hemoglobin (Hb) decreased significantly in both the donation and control groups, but differences within between groups were not significant at any time point ($p \geq 0.05$).Test subject mean Hb values were 14.6 and

14.0 g/dL on baseline day and donation day, respectively ($p < 0.05$), and those for the control group were 15.5 and 14.7 g/dL, respectively ($p < 0.05$).

DISCUSSION

In this study, we found that donation of 450 mL of blood after a strenuous military field exercise reduced VO_{2max} by 3.6%-11.2% compared to baseline values. The subjects in the control group did not display a similar decline in performance or VO_{2max} after the military exercise. Both results are in line with our expectations that losing 450 mL of blood will result in some degree of physical performance loss.

Donating blood increased submaximal HR during physical exercise in the donation group. Thus, both maximal and submaximal exercise performance were reduced after blood donation; however, ETT was not significantly different in either of the two groups either pre- or post-exercise, and this might be explained by the low numbers of participants.

The significant drop in VO_{2max} we found in the donation group correlates with the findings of Balke et al.,[5] who concluded in their 1954 paper that "Loss of blood in amounts customary in blood donation imposes significant limitations on physiological adjustments to severe exercise." This study has a time frame from blood donation to testing of 1 hour. Sixty years later, Gordon et al. examined 15 athletes on a bicycle test with incremental increase in resistance to volitional exhaustion after donation of 450 mL blood (6), reporting in 2014 that they found significant decreases in VO_{2max}compared to pre-donation exercise. Burnley et al. examined 11 young healthy males on a bicycle trial with incremental increase in resistance pre- and post-donation of 450 mL of blood (4), and recorded changes in VO_2 kinetics, ETT, and VO_{2max}. As in the above-mentioned studies, significant decreases in VO_{2max}-were noted between donation and control groups, and lower VO_{2max} after blood donation alone has been reported in multiple studies.[6-9] In every case, performance testing was delayed for 24 hours after donation, which allows Hb levels to decrease as a result of Starling forces, and thus normal circulating blood volume was reestablished before VO_{2max} was assessed. In a test of 10 male cyclists 2 hours post-donation of one unit of blood Panebianco et al. found that VO_{2max} performance decreased, but submaximal performance remained unchanged.[6] Because time between blood donation and testing was shorter (2 hr), this work was more similar to our study design; however, the method for measuring VO_{2max} differed, and thus results are difficult to compare.

The commonly accepted explanation for the decrease in VO_{2max} after blood donation is that Hb concentrations decrease, thus, as described by Fick's principle, delivery of oxygen (DO_2) during maximal performance is affected. Decreases in Hb concentrations were seen in both groups at the time of the posttest, most likely due to the effect of rehydrate fluids available to study participants during blood donation and the posttest blood sampling period. This study did not record the amount of fluid intake among study subjects before blood sampling, thus a full analysis is not possible. It is unlikely that the decrease in Hb concentrations can be explained by hemodillution after water intake in the timeframe between completion of exercise and blood sampling and we can neither rule out test variability, thus differences could not be fully explained at this time. The change in Hb may partly explain the decrease in VO_{2max} but it does not explain the differences between groups. Hb decreased in both groups, but the difference in VO_{2max} was limited to the donation group. A more likely explanation for the decrement in the donation group's VO_{2max} is that blood donation resulted in a reduction in circulation volume, with a concomitant reduction in venous return to the heart, and thus in reduced cardiac output and DO_2.

ETT was not significantly different in either the donation group or non-donation group between pre- and post-exercise testing. This finding was not consistent with that reported by Burnley et al. in 2006, which found a significant reduction in the time to exhaustion (of 54 sec or approx. 14%) after blood donation.[10] Possible reasons for the differences between that study and ours include that Burnley did not use a double-blinded study design, and our subjects were highly motivated Special Forces soldiers at peak physical condition. The low numbers of participants and the borderline p-value of 0.06 (9.5%) can also be of relevance to this difference from Burnley's work.

Factors that limit VO_{2max} were described by Bassett and Howley[18] in their seminal paper based on findings of A.V Hills published in the early 1920s. This work is often referred to as the "catastrophic model" because according to the authors, maximal exercise is eventually terminated due to a lack of oxygen delivery capacity to exercising muscle. The resulting anaerobic conditions that develop limit the production of ATP, causing muscle fatigue and eventual collapse. This model has been broadly criticized by Noakes et al.[19] who propose an alternative model termed the "Central Governor Model," with the main difference being the role of neural recruitment of skeletal muscle during exercise. Our test candidates were all Special Forces soldiers and they have been through extensive selection on skills like mental strength and stamina. This might affect their ability to perform under stress and thus affect their oxygen uptake by neural recruitment as explained by the "Central Governor Model."

Another difference in our population compared the normal population is both the weight and level of physical fitness. It has been shown that physical performance and bodyweight affects the blood volume, and thus the affect

of blood donation.[20] Due to these facts, our findings can probably not translate to the general population.

Conversely, HR at submaximal effort differed significantly in the donation group. This early change has not been previously reported and was not significant in the control group, although HR was significantly elevated in both groups at maximal effort. Potential reasons for the early changes in the donor population may be due to the reduction in blood volume resulting in reduced DO_2. During submaximal performance increased HR will compensate for the reduction in stroke volume to maintain DO_2. However, during maximal performance, and at maximal HR the reduction in stroke volume explains the change in peak performance between the two groups. Other studies may not have detected this early change due to longer intervals between donation and testing which allowed circulatory volumes to equilibrate. The closest comparator was the study design reported by Balke et al., who performed testing within 1 hour of blood donation. This study also detected a significant decrease in VO_{2max} after blood donation, but a change in HR was not reported. Gordon et al.[12] and Burnley et al.[10] performed post-donation testing at the 24 hours mark, after normovolemia was presumably established due to rehydration, and interstitial fluid shifts into the systemic circulation.

Our research group has previously found that VO_{2max}, rapid shooting skills and hiking performance are not compromised by blood donation. This study was conducted in a similar group of Special Forces soldiers, but not under duress but rather well fed and rested.[13] This study demonstrates that compensatory mechanisms are impaired under stress conditions, and loss of performance begins to occur.

These findings raise an important question, regarding whether the combined effects of reduced physical capacity and blood donation result in an unacceptable level of risk when donating blood under battlefield conditions. Ultimately, soldiers and care providers will have to make these determinations based on both medical and operational considerations; however, these study findings impart valuable information to assist operational decisions. While it is clear that implementation of a buddy transfusion protocol to provide WFWB for the resuscitation of severely bleeding casualties is not without risk, it is equally clear that even under stressful conditions Special Forces soldiers perform well and demonstrates that they can tolerate the loss of a unit of blood without compromising battle readiness. The shortest ETT time was 813 seconds, which is still a remarkably good result.

The limitations of this study include a small sample size, the lack of a method of estimating pulmonary artery pressure, and the ad libitum administration of rehydration fluids. In addition, the unique characteristics of these fit and motivated Special Forces soldiers limit generalizability of the study findings. Conversely, this study was not limited by open study group allocation, as was previous research evaluating the effect of blood donation on donor performance. Whereas the subjects in previous studies were not blinded and may have been influenced by awareness of their blood loss, donors and investigators in this study were not aware of study assignments. The lack of cognitive testing is another weakness of this study, and therefore we cannot make conclusions regarding cognitive performance after blood donation.

To our knowledge, this is the first study to implement blinding of both donors and investigators, there by strengthening the validity of the results.

Understanding effects of blood donation on submaximal performance in a combat setting is a valuable addition to information regarding maximal performance results. Special Forces personnel are more likely to perform at a submaximal level when on assignment, whereas maximal performance is infrequently required. Additionally, study conditions cannot model the actual maximal capacity in life-threatening conditions when these highly trained elite forces will likely recruit additional reserves due to a massive sympathetic response.

For non Special Forces and civilian health care workers a similar decrease in performance might even be more tolerable, thus allowing them to safely serve as emergency donors under extreme situations.

The authors would like to call for additional studies on this field with more general populations, including cognitive testing after blood donation. Walking blood banks and emergency donors can be of great benefit and donor safety is important is such a setting.

CONCLUSION

Donating blood after a week of strenuous physical activity is feasible for Special Forces soldiers. While the donation results in some diminishment of VO_{2max}, a 3.6%-11.2% decrease in relative VO_{2max}, and in elevation of submaximal HR levels, highly trained personnel continue to perform well both at both submaximal and maximal effort levels.

CONFLICT OF INTEREST

Heather Pidcoke is employed by Terumo BCT. The remaining authors declare that they have no conflicts of interest relevant to the manuscript submitted to TRANSFUSION.

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