Basics of Blood Management

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FIRST EDITION
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Contents

Preface to the first edition, vii
Acknowledgments, viii
Introduction, ix
1 History and organization of blood management, 1
2 Physiology of anemia and oxygen transport, 9
3 Anemia therapy I: erythropoiesis stimulating proteins, 21
4 Anemia therapy II (hematinics), 35
5 Growth factors, 50
6 Fluid therapy, 65
7 The chemistry of hemostasis, 77
8 Recombinant blood products, 96
9 Artificial blood components, 110
10 Oxygen therapy, 125
11 Preparation of the patient for surgery, 139
12 Iatrogenic blood loss, 160
13 The physics of hemostasis, 172
14 Anesthesia—more than sleeping, 191
15 The use of autologous blood, 200
16 Cell salvage, 211
17 Blood banking, 227
18 Transfusions. Part I: cellular components and plasma, 243
19 Transfusions. Part II: plasma fractions, 265
20 Law, ethics, religion, and blood management, 287
21 Step by step to an organized blood management program, 299

Appendix A: Detailed information, 322
Appendix B: Sources of information for blood management, 329
Appendix C: Program tools and forms, 334
Appendix D: Teaching aids: research and projects, 346
Appendix E: Address book, 350
Index, 376
Preface to first edition

The benefit-to-risk ratio of blood products needs constant evaluation. Blood products, as therapeutic agents, have had the test of time but lack the evidence we expect from other medicinals. Blood, an organ, is used as a pharmaceutical agent by the medical profession, due to the achievements in collection, processing, banking, and distribution. The fact that the most common risk of blood transfusion is blood delivery error supports the notion that blood is handled as a pharmaceutical agent. Over the last few decades, the risk of blood transfusion and associated complications has raised concerns about safety of blood by both the public and health-care providers. At the same time, experience with patients refusing blood and data on blood conservation brought to light the real possibility of other modalities to treat perisurgical anemia and to avoid it with blood conservation methods. In addition to risks and complications, data became available demonstrating the behavioral aspect of transfusion practice versus an evidence-based practice. In this book, the authors address many aspects of modern transfusion medicine, known blood conservation modalities, and new approaches to the treatment of perisurgical anemia, as well as special clinical considerations. This approach, now termed “blood management” by the Society for the Advancement of Blood Management, incorporates appropriate transfusion practice and blood conservation to deliver the lowest risk and highest benefit to the patient. In addition, it brings all these modalities to the patient’s bedside and above all is a patient-centered approach. Blood management is a multidisciplinary, multimodality concept that focuses on the patient by improving patient outcome, making it one of the most intriguing and rewarding fields in medicine.
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Introduction

The benefit-to-risk ratio of blood products needs constant evaluation. Blood products, as therapeutic agents, have had the test of time but lack the evidence we expect from other medicinals. Blood, an organ, is used as a pharmaceutical agent by the medical profession, due to the achievements in collection, processing, banking, and distribution. The fact that the most common risk of blood transfusion is blood delivery error supports the notion that blood is handled as a pharmaceutical agent. Over the last few decades, the risk of blood transfusion and associated complications has raised concerns about safety of blood by both the public and health-care providers. At the same time, experience with patients refusing blood and data on blood conservation brought to light the real possibility of other modalities to treat perisurgical anemia and to avoid it with blood conservation methods. In addition to risks and complications, data became available demonstrating the behavioural aspect of transfusion practice versus an evidence-based practice. In this book, the authors address many aspects of modern transfusion medicine, known blood conservation (SABM, www.sabm.org) modalities, and new approaches to the treatment of perisurgical anemia, as well as special clinical considerations. This approach, now termed “blood management” by the Society for the Advancement of Blood Management (SABM, www.sabm.org), incorporates appropriate transfusion practice and blood conservation to deliver the lowest risk and highest benefit to the patient. In addition, it brings all these modalities to the patient’s bedside and above all is a patient-centered approach. Blood management is a multidisciplinary, multimodality concept that focuses on the patient by improving patient outcome, making it one of the most intriguing and rewarding fields in medicine.

Blood management requires an understanding of all elements of blood and transfusions. It includes the philosophy, biology, physiology, and ethical considerations, as well as demonstrating the practical application of various techniques. This publication introduces the reader to blood management and explains how to improve medical outcomes by avoiding undue blood loss, enhancing the patient’s own blood, and improving tolerance of anemia and coagulopathy until any of these underlying conditions are successfully remedied.

This introduction to blood management is intended for the training and early practicing clinicians. It is meant to be both informative and practical and spans many of the medical specialties that encounter blood and transfusions as part of their daily practice. It will aid in tailoring individual care plans for the different patients. Finally, it addresses the structure and function of a blood management program, a novel approach to blood conservation, and improved patient outcome.

In this book, blood management is considered from an international perspective, so attention is paid to conditions encountered in developing as well as industrial countries. Techniques such as cell salvage are performed differently in economically deprived countries; HIV, hepatitis, and malaria may or may not be a threat to the blood supply, depending on geographic location; oxygen, intravenous fluids, and erythropoiesis-stimulating proteins may be readily available in some countries or inaccessible in others. The book is intended to broaden the readers’ horizons, discussing working conditions encountered by blood managers around the world. Many of the clinical scenarios and the exercise that follow are intended for the reader to adapt the information to the prevailing circumstances in their location.

This book is unique in the fact that it is the first dedicated in its entirety to the concept of blood management. The authors hope that this book will stimulate the readers to further advance blood management through shared experience and research. It is intended to be informative, practical, enjoyable and will stimulate debate and discussion as well as help patients in need.
With this introductory chapter the reader will be given a glimpse into the organization of blood management and its history—a history that is still extremely active and changes day to day.

**Objectives of this chapter**

1. Identify historical developments that led to today’s concept of blood management.
2. Demonstrate the benefits of blood management.
3. Identify blood management as “good clinical” practice.
4. Show that blood management and its techniques should be used in all cases that qualify.
5. Help understand how a blood management program works.

**Definitions**

*Bloodless medicine and surgery:* Bloodless medicine is a multimodality, multidisciplinary approach to safe and effective patient care without the use of allogeneic blood products. Bloodless medicine and surgery utilizes pharmacological and technological means as well as medical and surgical techniques to provide the best possible care without the use of donor blood.

*Transfusion-free medicine and surgery:* Since “bloodless medicine” is kind of a misnomer, the term “transfusion-free medicine” was coined and is used instead.

*Blood conservation:* “Blood conservation is a global concept engulfing all possible strategies aimed at reducing patient’s exposure to allogeneic blood products” [1]. This concept does not exclude the use of allogeneic blood entirely.

*Blood management:* Blood management is the philosophy to improve patient outcomes by integrating all available techniques to reduce or eliminate allogeneic blood transfusions. It is a patient-centered, multidisciplinary, multimodal, planned approach to patient care. Blood management is not an “alternative,” it is the standard of care.

**A brief look at history**

**History of bloodless medicine, transfusion-free medicine, blood conservation, and blood management**

The term “bloodless medicine” is often associated with the belief of Jehovah’s Witnesses to refrain from the use of blood, therefore ruling out the option of blood transfusion. The essence of bloodless medicine, and lately, blood management, however, is not restricted to the beliefs of a religious group. To get a better understanding as to what bloodless medicine and blood management means, let us go back to the roots of these disciplines.

One is not completely wrong to attribute the origin of the term “bloodless medicine” to the endeavor of Jehovah’s Witnesses to receive treatment without resorting to donor blood transfusion. Their attitude toward the sanctity of blood greatly influences their view of blood transfusion. This was published as early as 1927 in their journal *The Watchtower* (December 15, 1927). Although the decision to refuse blood transfusion is a completely religious one, the Witnesses frequently used scientific information about the side effects of donor blood transfusion. The booklet entitled *Blood, Medicine and the Law of God* (published in 1961) addressed issues such as transfusion reactions, transfusion-related syphilis, malaria, and hepatitis.

Refusing blood transfusions on religious grounds was not easy. Repeatedly, patients were physically forced to take donor blood, using such high-handed methods as
incapacitation by court order, strapping patients to the bed (even with the help of police officers), and secretly adding sedatives to a patient’s infusion. In the early 1960s, representatives of Jehovah’s Witnesses started visiting physicians to explain the reasons why transfusions were refused by the Witness population. Often, during the same visit, they offered literature which dealt with techniques that were acceptable to the Witness patients, informing physicians of the availability of the so-called transfusion alternatives. After a few years of work, the governing body of Jehovah’s Witnesses announced the formation of Hospital Liaison Committees (1979). These continued to “support Jehovah’s Witnesses in . . . their determination to prevent their being given blood transfusions, to clear away misunderstandings on the part of doctors and hospitals, . . . to establish a more cooperative spirit between medical institutions and Witness patients” and to “alert hospital staff to the fact that there are valid alternatives to the infusion of blood” (italics ours). Occasionally, the Witnesses even went to court to fight for their rights as patients. In a great number of cases, the Witnesses’ position was upheld by the courts.

Although many physicians had difficulty with the concept of bloodless medicine, there were some physicians who took up the challenge to provide the best possible medical care without the use of blood transfusions. These were in fact the earliest blood managers. As their experience in performing “bloodless” surgery increased, more complex procedures such as open heart surgery, orthopedic surgery, and cancer surgery could be performed. Even children and newborns could successfully be treated without transfusing blood. Not before long, those pioneering physicians published their results with Witness patients, thereby encouraging other doctors to adopt the methods used in performing such surgical interventions.

Among the first ones who rose to the challenge was the heart surgeon Denton Cooley of Texas. In the early 1960s, his team devised methods to treat Witness patients. Reporting on his early experiences, he published an article in a 1964 issue of The American Journal of Cardiology. In the article “Open heart surgery in Jehovah’s Witnesses” his team described the techniques used. In 1977, Cooley reported his experiences with more than 500 patients [2].

Cooley’s example was followed by many other courageous physicians. For instance, in 1970 Dr Pearce performed bloodless open heart surgery in New Orleans. His efforts did not go unnoticed. Newspapers reported on these spectacular cases. Perhaps out of curiosity or out of the earnest desire to learn, many colleagues visited Dr Pearce’s team in the operating room to learn how to do “bloodless hearts.” Dr Jerome Kay, from Los Angeles, also performed bloodless heart surgery. In 1973 he reported that he is now performing bloodless heart surgery on the majority of his patients. The call for bloodless treatments spread around the whole world. Dr Sharad Pandey of the KEM hospital in Mumbai, India, adopted bloodless techniques from Canada and tailored them to fit Indian conditions. Centers in Europe and the rest of the world started adopting those advances as well.

It is understandable that Witness patients preferred the treatment of physicians who had already proven their willingness and ability to treat them without using donor blood. The good reputation of such physicians spread and so patients from far away were transferred to their facilities. This laid the foundation for organized “bloodless programs.” One of the hospitals with such a program was the Esperanza Intercommunity Hospital in Yorba Linda, California, where a high percentage of patients were Witnesses. Dr Herk Hutchins, an experienced surgeon and a Witness himself, was known for his development of an iron-containing formula for blood-building. Among his team was the young surgeon Ron Lapin. Later, he was famed for his pioneering work in the area of bloodless therapies. Critics labeled him a quack. Nevertheless, he continued and was later honored for opening one of the first organized bloodless centers in the world, as well as for publishing the first journal on this topic, and for his efforts to teach his colleagues. During his career, he performed thousands of bloodless surgeries.

All of those pioneers of blood management had to rise to the challenge of using and refining available techniques, adjusting them to current needs, and individualizing patient care. They adopted new technologies as soon as this was reasonable. Much attention was paid to details of patient care, thus improving the quality of the whole therapy. They also fought for patients’ rights and upheld those rights. Many involved in the field of blood management confirm the good feeling of being a physician in the truest sense. There is no need to force a particular treatment. Such an attitude is a precious heritage from the pioneers of blood management. Now, at the beginning of the twenty-first century, this pioneer spirit can still be felt at some meetings dedicated to blood management.

Military use of blood and blood management

Over the centuries, the armies of different nations contributed to what is now available for blood management, but not on religious grounds. It can actually be said that
the military made many crucial contributions to blood management by taking care of the thousands of wounded operated on before transfusions became feasible. In fact, every surgery performed before the era of blood transfusion was, strictly speaking, a “bloodless surgery.” Surgeons were confronted with blood loss, but had no way to replace blood. This meant it was imperative to stop hemorrhage promptly and effectively and to avoid further blood loss. During the centuries, battlegrounds were the places where surgeons were massively confronted with blood loss and it was on the battlefield that hemorrhage was recognized as a cause of death. Hemorrhaging victims needed surgery. It was then that techniques of bloodless medicine and blood management were invented. The experience of the early surgeons serving near the battlefield is applicable in today’s blood management schemes. William Steward Halsted, a surgeon on the battlefield, described uncontrolled hemorrhage [3] and later taught his trainees at Johns Hopkins the technique of gentle tissue handling, surgery in anatomic ways, and meticulous hemostasis (Halstedian principles). His excellent work provides the basis of the surgical contribution to a blood management program.

As soon as transfusions became somewhat practical, the military used them for their purposes. Since war brought about a deluge of hemorrhaging victims, there was a need for a therapy. The First World War brought the advent of blood anticoagulation. This made it possible to transport blood to the wounded and reduced the use of living donors in the field. But there were other problems. Storage times and problems with logistics called for improvements in blood therapy. During the Second World War, the problem of storage of blood was partly overcome by the advent of blood banks. Another development was due to Cohn’s fractionation of blood, which led to the production of plasma as a volume expander for war victims. The United States extensively used plasma for volume expansion in World War II.

Although the World Wars propelled the development of transfusion medicine, these simultaneously propelled the development of alternative treatments. Tremendous problems with availability and logistics as well as with compatibility of blood made transfusions near the battlefield dangerous, difficult, and expensive. Those problems, as well as inherent risks of transfusions, led to the search for other ways of treatment. Intravenous fluids had been described in earlier medical literature [4, 5], but the pressing need to replace lost blood and the difficulties involved in transfusions provided a strong impetus for military medicine to change practice. In this connection, note the following report appearing in the Providence Sunday Journal of May 17, 1953: “The Army will henceforth use dextran, a substance made from sugar, instead of blood plasma, for all requirements at home and overseas, it was learned last night. An authoritative Army medical source, who asked not to be quoted by name, said ‘a complete switchover’ to the plasma substitute has been put into effect, after ‘utterly convincing’ tests of dextran in continental and combat area hospitals during the last few months. This official said a major factor in the switchover to dextran was that use of plasma entails a ‘high risk’ of causing a disease known as serum hepatitis—a jaundice-like ailment. Not all plasma carries this hazard, he emphasized, but he added that dextran is entirely free of the hazard. ‘We have begun to fill all orders from domestic and overseas theaters with dextran instead of plasma.’”

Efforts to develop another “blood substitute” were intensified by US military in 1985. Major investments supported research, either by contract laboratories or by military facilities themselves [6]. This time, not the search for a plasma expander but the search for an oxygen carrier was the driving force behind the army’s efforts.

Promising products in the sector of blood management were readily introduced to the military. One example is a cell-saving device. The surgeon Gerald Klebanoff, who served in the Vietnam War, introduced a device for autotransfusion in the military hospitals. Another example is the recombinant clotting factor VIIa. Although officially declared to be a product for use in hemophiliacs, the Israeli army discovered its potential to stop life-threatening hemorrhage and therefore included it in their treatment of injured victims.

Also, in recent times, the military showed a keen interest in blood management. After the attack on the World Trade Center in New York on September 11, 2001, physicians of the US military approached the Society for the Advancement of Blood Management and asked about blood management. They were aware that a war in a country like Afghanistan would also require preparation on the part of the physicians. The high costs of transfusions in war times (up to US $9000 must be calculated for one unit of red blood cells when transfused in countries like Afghanistan) and logistic difficulties called for blood-conserving approaches. Consequently, specialists in the field of blood management met together with representatives of the US military, the result of which was an initiative named STORMACT® (strategies to reduce military and civilian transfusion). The consensus of this initiative was a blood management concept to be used to treat victims of war and disaster as well as patients in a preclinical setting.
Transfusion specialists support blood management

Interestingly, right from the beginning of transfusion medicine, the development of blood transfusion and transfusion alternatives were closely interwoven. “Alternatives” to transfusion are as old as transfusion itself.

The first historically proven transfusions in humans were performed in the seventeenth century. The physicians were aiming to cure mental disorders rather than the substitution of lost blood. But the very first transfusion specialists were in fact also the first people to try infusions that were later called transfusion alternatives. For instance, it was reported that Christopher Wren was involved in the first transfusion experiments. He was also the first to inject asanguinous fluids, such as wine and beer. After two of Jean Baptiste Denise’s (a French transfusionist) transfused patients died, transfusion experiments were prohibited in many countries. Even the Pope condemned those early efforts. For a long time, transfusions came to a halt.

In the beginning of the nineteenth century, the physician James Blundell was looking for a method of prohibiting the death of female patients due to profuse hemorrhage related to childbirth. His amazing results with retransfusion of the women’s shed blood rekindled the interest of the medical community in transfusion medicine. Due to his work with autotransfusion he was named in the list of the “fathers of modern transfusion medicine.” This demonstrates again that transfusion medicine and alternatives to allogeneic transfusion are closely related.

After Blundell demonstrated that retransfusion of shed blood saved lives, other physicians followed his example. This gave new impetus to transfusion medicine, and in 1873 Jennings [7] published a report of about 243 transfusions in humans, of which almost half of the cases died. Allogeneic transfusions remained dangerous. Blood groups were not known at that time. Technical problems with the transfusion procedure itself resulted in complications and effective anticoagulants were still unknown. Frustration around this situation led some researchers to look for alternative treatments in the event of hemorrhage. Barnes and Little came up with normal saline as a blood substitute [8]. Hamlin tried milk infusions [9]. The use of gelatin was also experimented with. But soon, normal saline was introduced into medical practice. One of the advocates of normal saline, W.T. Bull, wrote in 1884 [10]: “The danger from loss of blood, even to two-thirds of its whole volume, lies in the disturbed relationship between the caliber of the vessels and the quantity of blood contained therein, and not in the diminished number of red blood corpuscles; and … this danger concerns the volume of the injected fluids also, it being a matter of indifference whether they be albuminous or containing blood corpuscles or not.”

In the early 1900, Landsteiner’s discovery of the blood groups was probably the event that propelled transfusion medicine to where it is today. Some 10–15 years later, when Reuben Ottenberg introduced routine typing of blood into clinical practice, the way was paved for blood transfusions. About that time, technical problems had been solved by new techniques and anticoagulation was in use. Russian physicians (Filatov, Depp, Yudin) stored cadaver blood. The groundwork for the first blood bank was laid in 1934 in Chicago by Seed and Fantus [11], and as already mentioned, the wars of the first half of the twentieth century brought about changes in transfusion medicine. After two World Wars the medical community had a seemingly endless and safe stream of blood at their disposal. Adams and Lundy published an article, suggesting a possible transfusion trigger of a hemoglobin level of 10 mg/dL and a hematocrit of 30. For nearly four decades thereafter, physicians transfused to their liking, convinced that the benefits of allogeneic transfusions outweigh their potential risks.

As time went by, reports about blood-borne diseases increased. In 1962, when the famous article of J.G. Allen [12] again demonstrated a connection between transfusion and hepatitis, an era of increased awareness about transfusion-transmissible diseases began. But the risk of hepatitis transmission did not concern the general medical community, and it became an acceptable complication of banked blood. It was not until the early 1980s that the medical community and the public became aware of the risks of transfusions. The discovery that an acquired immunodeficiency syndrome was spread by allogeneic transfusion heightened public awareness, and the demand for safer blood and bloodless medicine increased. Other problems with allogeneic transfusions such as immunosuppression added to the concerns. Again, as in the centuries before, it was the ones concerned most about transfusion issues who were looking for alternative approaches. Lessons learned from the work with the Jehovah’s Witnesses community were ready to be applied on a wider scale. In the United States, the National Institute of Health launched a consensus conference on the proper use of blood. The Adams and Lundy’s 10/30 rule was revised, and it was agreed upon that a hemoglobin level of 7 mg/dL would be sufficient in otherwise healthy patients.

With time, the incentives for better blood management and blood conservation change. The role of immunomodulation with allogeneic blood is controversial but, nonetheless, offers a reason for blood conservation;
the incremental increase of blood products is another and
lastly, sporadic but serious blood shortages are all good
reasons to consider effective blood management.

**Blood management today and tomorrow**

Currently, there are more than 100 organized bloodless
programs in the United States. Many are transitioning to
become blood management programs. This is not unique
to the United States since many more programs have been
established worldwide. Most of them were formed as a
result of the initiatives of Jehovah’s Witnesses. However,
a growing number of those programs have now realized
the benefits that all patients can receive from this care.
The increasing number of patients asking for treatment
without blood demonstrates a growing demand in this
field. Concerns about the public health implications of
transfusion-related hazards have led governmental insti-
tutions, around the globe, to encourage and support the
establishment of these programs.

The growing interest in blood management is reflected
by these activities described herein. Major medical orga-
nizations (e.g., the American Association of Blood Banks,
AABB) are now including blood management issues on
the agenda of their regular meetings. Many transfusion
textbooks and regular medical journals have incorporated
the subject of blood management in their publications.
A growing body of literature invites further investigation
(compare Appendix B). In addition, professional societies
dedicated to furthering blood management were founded
throughout the world. It is their common goal to provide
a forum for the exchange of ideas and information among
professionals engaged in the advancement and improve-
ment of blood management in clinical practice. This is
done by facilitating cooperation among existing and fu-
ture programs for blood conservation, transfusion-free or
bloodless medicine and blood management; also, by re-
inforcing the clinical and scientific aspects of appropriate
transfusion practice, by encouraging and developing ed-
ucational programs for health-care professionals and the
public, and by contributing to the active continuing med-
ical education of its members. Usually, interested persons
from a variety of medical and nonmedical backgrounds
are invited to participate.

Clearly, out of humble beginnings as an outsider spe-
cialty, blood management has evolved to be in the main-
stream of medicine. It improves the outcome for the
patient, reduces costs, and brings satisfaction for the
physician—a clear win–win situation. Blood management
is plainly good medical practice.

What are the future trends in blood management? As
long as there is a need for medical treatment, blood man-
agement will develop. Many new drugs and techniques
are on the horizon. To date, there are many techniques
available to reduce or eliminate the use of donor blood
that it is not necessary to wait for the future. A commit-
tment to blood management is what will change the way
blood is used. The authors of this book hope that the in-
formation provided by its pages will be another piece in
the puzzle that will eventually define future blood man-
agement by a new generation of physicians.

**Blood management as a program**

The organized approach to blood management is a
program. These programs are named according to the
emphasis each one puts on different facets of blood man-
agement, such as bloodless programs, transfusion-free
programs, blood conservation programs, or global blood
management programs. No matter what a hospital calls its
program, there are some basic features that good quality
programs have in common.

**The administration**

The basis for establishing a program is not primarily a fi-
nancial investment but rather a great deal of commitment
on the part of the hospital. Administration, physicians,
nurses, and other personnel need to be involved. Only
the sincere cooperation of those involved will make a pro-
gram successful.

The heart and soul of a program is its coordinator
with his/her in-hospital office [13, 14]. As a historical
prospective, coordinators are often members of Jehovah’s
Witnesses. However, as such programs are more widely
accepted, there is an increasing number of coordinators
with other backgrounds. Usually, coordinators are em-
ployed and paid by the hospital.

During the initial phases of development of the pro-
gram, the coordinators may be burdened with significant
workload. Together with involved physicians, the coordi-
nator has to recruit additional physicians who are willing
and able to participate in the program. Since successful
blood management is a multidisciplinary endeavor, spe-
cialists from a variety of fields need to be involved. (What,
for instance, is the use of a dedicated anesthesiologist if
surgeons do not participate?) The coordinator meets with
the heads of the clinical departments and works toward
mutual understanding and cooperation. Each physician
willing to participate needs to meet with the coordinator to affirm the physician’s commitment to the program and to enhance his/her knowledge of basic ethical and medical principles involved. To ensure a lasting and dependable cooperation between physicians and the program, both parties sign a contract. This contract outlines the points that are crucial for blood management with its legal, ethical, and medical issues.

The coordinator is also instrumental for the initial and continuous education of participating and incoming staff. She/he may use in-service sessions, invite guest speakers, collect and distribute current literature, get information on national and international educational meetings, and help staff interested in hands-on experience in the field of blood management. Ideally, participating staff members take care of their education themselves and contribute to the success of the program.

From the beginning of the program, there needs to be a set of policies and procedures. Guidelines as to cooperation with other staff members need to be worked out. It is prudent to have the hospital lawyer review all such documents. Each individual hospital must find a way to educate patients, document their will, and make sure that patients are treated according to their will and they are clearly identifiable. Transfers of patients to and from the hospital need to be organized. A mode of emergency transferal needs to be established. Procedures already in existence such as storage and release of blood products and rarely used drugs for emergencies need to be reviewed. Most probably, there are many medical procedures already available in the hospital that just need to be adapted to the needs of the program. Additional blood management procedures and devices are to be introduced to the hospital staff. The use of hemodilution, cell salvage, platelet sequestration, autologous surgical glue, and other methods needs to be organized. Besides, departments not directly involved in patient care can contribute to the development of policies and procedures. This holds true for administrative offices, the blood bank, laboratory, technical department, pharmacy, and possibly the research department. There are also a variety of issues that need legal and ethical clarification. In keeping with national and international law, issues involved with pediatric and obstetric cases need to be clarified well before the first event arises. Forms need to be developed and a protocol for obtaining legal consent and/or advance directive must be instituted.

To assure continuing support on the part of the administration and the public, some measures of quality control and assurance need implementation. Statistical data from the time before the establishment of a certain procedure should be available for comparison with those obtained after its institution and during the course of its implementation. This is a valuable instrument to demonstrate the effectiveness of procedures and their associated costs. It also serves as an aid in decision making regarding possible and necessary changes. If records are kept up-to-date, developments and trends can be used as an effective tool for quality assurance and for the identification of strong and weak points in a program. Such records are also helpful for negotiations with sponsors and financial departments, discussions with incoming physicians, and for public relations.

The coordinators, and later their staff, need to be well informed about policies and procedures in their hospital and the level of care the facility can provide. There may be times when burden of cases or the severity of a patient’s condition outsize the faculty’s capacity or capability. In such cases, a list of alternative hospitals better suited to perform a certain procedure should be available.

Good communication skills are essential for the daily activities of the coordinator since he/she is the link between patients and physicians. The coordinator is in constant contact with the patient and his/her family and is involved in the development of the plan of care of every patient in the program. The coordinator informs the staff involved in the care of the patient about issues pertaining to blood management. In turn, staff members inform the coordinator about the progress of the patient. Planned procedures are discussed and any irregular development is reported. Thus, developing problems can be counteracted at an early stage, thereby avoiding major mishaps.

There is virtually no limit to the ingenuity of a coordinator. She/he is a pioneer, manager, nurse, teacher, host, helper, and friend. No successful program is possible without a coordinator. The last chapter in this book will further describe how the coordinator can work effectively for the development of a blood management program.

The physician’s part

Several studies on transfusion practice in relation to certain procedures demonstrate a striking fact: A great institutional variability exists in transfusion practice, for no medical reason. For example, in a study on coronary bypass surgery the rate of transfusions varied between 27 and 92% [15]. What was the reason? Did physicians who transfused frequently care for sicker patients? No, the major differing variable was the institution—and with it were the physicians. This is in fact good news. If the physician’s behavior can be modified to appropriately limit the
transfusion rate, then a blood management program can effectively reduce transfusions.

Basic and continuous education is crucial for physicians participating in a blood management program. To start with, physicians should intercommunicate about currently available techniques of blood management which relate to their field of practice and compare their own knowledge and skills with others. The result of such an honest comparison identifies the strong and weak areas in their practice of blood management. Then, new approaches, techniques, and equipment should be added as needed. However, remember that not all techniques fit all physicians and not all physicians fit all techniques. After all, it is not a sophisticated set of equipment that makes good blood management—it is a group of skilled physicians. That is why it is desirable that all physicians in a blood management program be aware of the experiences and skills of their colleagues, in order to make these available to the patients.

Another group of professionals that is essential for the program to succeed are the nurses. Nurses play a vital role as they contribute much to patient identification, education, and care. Nursing staff must therefore also be included in the process of initial and continuing education.

Commitment, education, cooperation, and communication are key factors for a successful blood management program. To make each treatment a success, it requires the concerted effort by physicians, coordinators, nurses, administration, and auxiliary staff on the one side, and the patient with his/her family on the other.

Key points

- Blood management is a good clinical practice that should be applied for all patients.
- Blood management is best practiced in an organized program.
- Blood management improves outcomes, is patient centered, multidisciplinary, and multimodal.
- Respect for patients, commitment, education, cooperation, and communication are the cornerstones blood management builds on.

Questions for review

- What role did the following play in the development of modern blood management: Jehovah’s Witnesses, physicians, the military, and transfusion specialists?
- What do the following terms mean: bloodless medicine, transfusion-free medicine, blood conservation, blood management?
- What are the important facets of a comprehensive blood management program?

Suggestions for further research

What medical, ethical, and legal obstacles had early blood managers to overcome? How did they do so? What can be learned from their experience?

Exercises and practice cases

Read the article of Adams and Lundy that builds the basis for the 10/30 rule.

Homework

Analyze your hospital and answer the following questions:
- What measures are taken to identify patients?
- What is done to comply with legal requirements when it comes to documentation of patients’ preferences for treatment?
- What steps are taken to ensure the patients’ wishes are heeded?

References

Tolerance of anemia while it is being treated is one of the cornerstones of blood management. This chapter explains the physiological and pathophysiological mechanisms underlying the body’s oxygen transport and use of oxygen. This will help to understand how the body deals with states of reduced oxygen delivery and efforts to increase delivery. Furthermore, it enables the reader to reflect critically on current and future therapeutic measures to increase oxygen availability to tissue.

Objectives of this chapter

1 Review factors that influence oxygen delivery.
2 Learn how to calculate oxygen delivery and consumption.
3 Identify mechanisms the body uses to adapt to acute and chronic anemia.
4 Define the vital role of the microcirculation.
5 Describe tissue oxygenation and tissue oxygen utilization.

Definitions

Anemia: Anemia is a reduction in the total circulating red blood cell mass, usually diagnosed by a decrease in hemoglobin concentration. Thresholds for anemia depend on the age and gender of the patient. Typically, anemia is said to exist in an adult male when hemoglobin is below 13.5 g/dL. In adult females, anemia is diagnosed when the hemoglobin is below 12 g/dL.

Regular physiology

A single equation describes the whole concept... Let us jump right into the subject, using the well-known equation where oxygen delivery is simply calculated by multiplying the cardiac output by arterial oxygen content.

\[ \text{DO}_2 = Q \times (\text{Hgb} \times 1.34 \times \text{SaO}_2 + 0.003 \times \text{PaO}_2) \times 10^1 \]

where \( \text{DO}_2 \), oxygen delivery; \( Q \), flow in L/min; \( \text{Hgb} \), hemoglobin in g/dL; 1.34, Hufner’s number; \( \text{SaO}_2 \), oxygen saturation of hemoglobin in %; 0.003, oxygen solubility in plasma; \( \text{PaO}_2 \), partial pressure of oxygen in arterial blood in mm Hg.

The equation describes the concept of systemic oxygen transport (macrocirculation), the knowledge of which constitutes a sound basis for understanding therapeutic interventions that enhance oxygen delivery.

One of the crucial factors of oxygen transport is the flow (\( Q \)) or cardiac output (\( \text{CO} \)), which is determined by the stroke volume (\( \text{SV} \)) and the heart rate (\( \text{HR} \)) (\( \text{CO} = \text{SV} \times \text{HR} \)). Flow is permanent for oxygen delivery since neither red cells nor any other blood constituent would reach their target if sufficient flow were lacking.

Another crucial player in oxygen transport is hemoglobin. In healthy individuals, most of the oxygen in blood is bound to hemoglobin. One molecule of hemoglobin can hold a maximum of four oxygen molecules. In vivo, 1 g hemoglobin has the potential to bind approximately 1.34 mL oxygen (Hufner’s number). In order to know exactly how much oxygen is bound to
hemoglobin, another variable must be known. This is the oxygen saturation (SaO2), the percentage of hemoglobin molecules that actually have bound oxygen.

Besides the oxygen bound by hemoglobin, a small amount of oxygen is physically dissolved in plasma. This amount is linearly dependent on the partial pressure of oxygen “above” the plasma, namely the inspiratory oxygen fraction (FiO2). The higher the FiO2, the more oxygen is dissolved. The amount of oxygen physically dissolved in plasma also depends on the specific Bunsen solubility coefficient α of oxygen. A Bunsen solubility coefficient of 0.024 means that there is 0.024 mL oxygen dissolved in 1 mL blood at normal body temperature (37°C) at a pressure of 1 atm. Using the Henry Dalton equation, it can be calculated that 0.003 mL O2/mL blood is physically dissolved in normal arterial blood (PO2 = 95 mm Hg, PCO2 = 40 mm Hg). Thus, the number 0.003 in eqn. (1) is the amount of physically dissolved oxygen in the blood under “normal” conditions. Although the amount of physically dissolved oxygen might appear insignificant compared to the amount of oxygen transported by hemoglobin, it should be borne in mind that every single molecule of oxygen bound to hemoglobin had to be physically dissolved in blood before it entered the red cell. Later it will be shown that the amount of physically dissolved oxygen is crucial for patients with severe anemia.

A single equation describes the whole concept... does it?

Imagine a patient with a very low serum calcium level. What treatment should be used? Substituting the body’s calcium stores sounds reasonable, but a doctor could also prescribe the patient pebbles and ask him/her to swallow them. The body’s content of calcium would certainly increase dramatically. Most would object, “But that is complete nonsense,” and they would be right, because it is obvious that the calcium contained in the pebbles does not reach the place where it is needed and cannot be used by the body. On the contrary, it may even cause harm to the patient.

The same holds true for patients suffering from a lack of oxygen carrying red cells. Initially the idea of filling the patient up may sound reasonable. However, the main point is easily overlooked if only macrocirculatory oxygen delivery is kept in mind; namely, Do I reach the goal of delivering oxygen to the tissue? And one step further: Do I succeed in maintaining aerobic metabolism? Just increasing the hemoglobin level by transfusing may, at times, be similar to feeding a stone to a patient with low calcium level. A number is changed, but the condition is not improved. For this reason the second half of oxygen delivery needs to be taken into consideration: the microcirculation.

How do red cells take up oxygen?

How about accompanying red cells on their journey through the human body. The trip starts in the capillary bed of the lungs. Here is where the red cells deliver carbon dioxide and take up oxygen.

Pulmonary gas exchange is governed by Fick’s law of diffusion, stating that the flux of diffusing particles (here oxygen and carbon dioxide) is proportional to their concentration gradient. Driven by this gradient, oxygen and carbon dioxide molecules move across membranes in the lung, in vessel walls and red cells, as well as through fluids in random walk. Due to the immense surface of the lung across which oxygen and carbon dioxide gradients develop, the exchange of oxygen and carbon dioxide is performed rapidly. Hemoglobin molecules further support the uptake of oxygen by red cells as hemoglobin molecules diffuse within the cell, also following a gradient. Once hemoglobin is oxygenated by means of oxygen diffusion across the red cell membrane, the oxygenated hemoglobin diffuses into the center of the red cell whereas deoxyhemoglobin diffuses toward the cell membrane, ready for oxygen uptake.

The processes of carbon dioxide release and oxygen uptake interact closely. As the partial pressure of carbon dioxide decreases, the affinity of hemoglobin for oxygen increases (Haldane effect). This effect supports the oxygenation of red cells in the lung.

The rate of oxygen uptake by human red cells is approximately 40 times slower than the corresponding rate of oxygen combination with free hemoglobin. The reason being that the hemoglobin in red cells is surrounded by several layers: cytoplasm, cell membrane, and a fluid layer adjacent to the red cell membrane. Oxygen therefore has to diffuse over a long distance before it can penetrate the cell. In particular the unstirred layers around the red cell pose a barrier to oxygen uptake. The impact of the red cell membrane to resist gas exchange is a subject of controversy and may in fact be negligible [1, 2]. The uptake of oxygen by red cells appears mainly to depend on the thickness of unstirred fluid layers [1] (and less on pH, 2,3-diphosphoglycerate (2,3-DPG) level, and membrane resistance).
How do red cells reach the microvasculature in the tissue?

Let us follow the red cells even further. As already described, they brought CO₂ for exhalation to the lung and have taken up oxygen. Now the red cells are ready for their next mission. They have to travel to the microcirculation to deliver the oxygen.

As the blood is impelled by the heart, it is urged from large vessels into the narrower areas of the human vasculature. The red cells then slow down. The resulting reduction in red cell velocity leads to a reduction in hematocrit in a determined segment of vessel relative to the hematocrit of blood entering or leaving the tube. This dynamic reduction of the intravascular hematocrit is called the Farhaeus effect [3]. The hematocrit in the microcirculation is about 30% of that in the systemic circulation and it remains constant until the systemic hematocrit is lowered to less than 15% [4].

As the red cells travel down the road toward the smallest capillaries, they tend to aggregate and build “rouleaux” formations, which look like stacks of coins [3]. This is due to macromolecular bridging and osmotic water exclusion from the gap between neighboring red cell membranes. Red cells line up in the center of the vessel where they have the maximum velocity. A plasma layer at the vessel wall works as kind of a lubricant to help the cells pass through the capillary. This arrangement of cells and plasma leads to a marked reduction in the viscosity so that blood viscosity in the microcirculation is close to that of plasma [3]. This effect was described by Farhaeus and Lindqvist when they wrote, “Below a critical point at a diameter of about 0.3 mm the viscosity decreases strongly with reduced diameter of the tube” [5].

The smallest capillaries have a diameter of less than 3 μm, and red cells a diameter of about 7–8 μm. Red cells are therefore much bigger than the roads they have to travel, but this poses no real problem since red cells are as soft as a sponge and are easily deformable. They virtually squeeze through the capillaries. It is obvious, then, that red cell deformability is essential for the perfusion of the microcirculation [6].

Now, the red cells have arrived in the microcirculation and are eager to give their oxygen to the tissues. But where exactly? Formerly, the Krogh model was used to explain tissue oxygenation. It described a single capillary with a surrounding cylinder of tissue. Oxygen gradients between the tissue and the vasculature were thought to be the driving forces of tissue oxygenation. Capillaries were the only structures thought to participate in the oxygen exchange with the tissue. Tissue sites farthest away from the capillary got the least oxygen. More recent research, however, has revealed that tissue oxygen distribution is even in all parts of tissue between vessels. The capillary—tissue oxygen gradient is very low, namely only about 5 mm Hg. Capillaries are nearly at equilibrium with the tissue and deliver oxygen to pericapillary regions only [7]. Thus, capillaries do not contribute significantly to tissue oxygenation. Most of the oxygen is delivered to the tissues via arterioles. Oxygen gradients were found to be greatest between arterioles and the tissue. Significant amounts of oxygen (30%) leave the vessels already at the arteriolar level. This is surprising since the tissue surrounding the arterioles does not have a metabolic demand high enough to justify an uptake of great oxygen amounts. In fact, only 10–15% of the losses can be explained by the oxygen consumption of the tissue surrounding the arterioles. There is no good explanation of where the other 85–90% of the oxygen remains. Probably, this oxygen serves the high metabolic demand of the endothelium [7]. Such demand may be explained by the enormous amount of endothelial synthesis (e.g., nitric oxide (NO), renin, interleukin, prostaglandins, and prostacyclin, etc.), transformation (of bradykinin, angiotensin, etc.), and constant work to adjust vascular tone.

Before continuing the trip with the red cells, let us step back and have a look at the whole microcirculation. Tissue as a whole depends on a network of capillaries (microvasculature), not only for delivery of oxygen but also for removal of metabolites. According to Fick’s law, the size of the area of diffusion is one main component in the exchange of oxygen and metabolites. In the microcirculation, the area of diffusion depends on the number of vessels available for exchange. The term “functional capillary density” (FCD) has been coined to describe the “size” of the microvasculature. This term refers to the number of functional, that is, perfused, capillaries per unit tissue volume [8]. Decreased FCD lowers tissue oxygenation uniformly (without causing oxygenation inhomogeneity) [7] and is associated with poor outcome.

To maintain tissue survival, adequate FCD is essential. Several factors modify FCD. The diameter of the capillaries depends on the surrounding tissue and internal pressure. This means that capillaries embedded in tissue cannot increase their diameter but they can collapse if they are not properly perfused. Sufficient arterial pressure and an adequate volume status are therefore needed for capillary perfusion. Another factor that modifies FCD and capillary blood flow is the metabolic requirement of the tissue.
tissue. Demand increases blood flow and excess of oxygen decreases blood flow. This mechanism is partially mediated by NO. Hemoglobin is able to scavenge NO and, therefore, constrict vessels. Hence, it seems red cells counteract their own work of delivering oxygen by blocking (constricting) their own road (vessels). This is not the case, however. The explanation for this phenomenon lies in the fact that hemoglobin comes in two different forms: R (relaxed, with high oxygen affinity) and T (tense, with low oxygen affinity). In the R form, hemoglobin not only transports oxygen but can also take up an NO compound (= S-nitrosylation). When the hemoglobin arrives at precapillary resistance vessels, it loses some oxygen and starts its transition from R to T. This change liberates the NO and causes dilatation of the arterioles [9]. With this mechanism, oxygen-loaded red cells open their doors to the tissue in order to deliver oxygen.

How do red cells give oxygen and how is it taken up by tissue?

The quantity of oxygen released by red cells depends much on the oxygen affinity of hemoglobin molecules. It is this affinity that translates oxygen flow into available oxygen. A common method to depict the behavior of hemoglobin is the oxygen dissociation curve (Fig. 2.1). The oxygen dissociation curve is sigmoid-shaped. This is due to conformational changes in the hemoglobin molecule that occur when it loads or releases oxygen. The uptake of each oxygen molecule alters the hemoglobin conformation and so it enhances the uptake of the next oxygen molecule. A change in the hemoglobin’s oxygen affinity profoundly affects oxygen release to the tissue, whereas the oxygen uptake by hemoglobin is scarcely affected.

There are several factors that per se can influence the hemoglobin’s affinity for oxygen (Fig. 2.1). Those factors include temperature, CO₂, H⁺, and 2,3-DPG [10]. Red blood cells deliver oxygen to metabolically active tissues. Such tissues release CO₂ that diffuses into the red cells. By carbonic anhydrase, CO₂ and H₂O react to H⁺ and HCO₃⁻. The resulting HCO₃⁻ is exchanged with extracellular Cl⁻, which leads to an intracellular acidification. The resulting decrease in pH facilitates oxygen dissociation from hemoglobin. Also, 2,3-DPG, a glycolytic intermediate, binds to deoxyhemoglobin and stabilizes hemoglobin in the deoxy form, thus reducing hemoglobin’s oxygen affinity and supporting oxygen release. In fact, this 2,3-DPG is so important that no oxygen can be unloaded by the red cells if it is completely lacking.

After being released from the hemoglobin molecule, oxygen has to pass several layers until it reaches the tissue. In contrast to oxygen uptake by red cells, release of oxygen depends mainly on the affinity of hemoglobin in the red cell and not so much on the thickness of surrounding unstirred fluid layers [1]. Deoxygenation therefore depends on pH and 2,3-DPG (lowered pH and increased 2,3-DPG levels facilitate release of oxygen) [1]. Only at very low hemoglobin concentrations chemical reactions limit release of oxygen from hemoglobin.
After the oxygen is released by the hemoglobin and has passed all barriers on its way to the tissue, the mitochondria accept the delivered oxygen molecules. Oxygen may have traveled via free flow or by means of a “coach” to a myoglobin molecule. The latter is called myoglobin-facilitated oxygen diffusion. “Deoxymyoglobin captures oxygen immediately as it crosses the interface: the newly formed oxymyoglobin diffuses away... The effect is to make the oxygen pressure gradient from capillary lumen to the sarcoplasm more steep, thereby enhancing the oxygen flux” [11]. This effect maintains oxygen flow to the mitochondria under conditions of low extracellular oxygen pressure.

Does the tissue use oxygen?

The human body depends on oxygen for adenosine triphosphate (ATP) generation and maintenance of aerobic metabolism. ATP, the body’s main energy source, is generated in the mitochondria using molecular oxygen. Only if the mitochondria actually use the oxygen, offered oxygen can do its job. This means that oxygen utilization is defined by the mitochondria.

Interestingly, there is a genetic component to the work of the mitochondria. Inherited or acquired changes in the enzyme supply determine how effectively oxygen can be used. Drugs such as propofol, which inhibit oxidative phosphorylation, can influence the mitochondria and thus the use of delivered oxygen [12]. Other factors influence tissues’ (and mitochondria’s) use of oxygen as well. The energy demand of the tissue influences how much oxygen is used. In turn, factors that influence the tissue’s metabolism also influence the rate of its oxygen use. NO inhibits mitochondrial respiration, and thus oxygen consumption. On the other hand, lack of NO increases metabolism and tissue oxygen consumption [13]. The influence of the body temperature on oxygen extraction is well known: Higher body temperature increases oxygen demand, extraction [14], and utilization. There are many more factors that alter the body’s energy requirement and thus the oxygen demand of the tissue: physical activity, hormones (catecholamines, thyroid hormones), infections, psychological stress, pain and anxiety, digestion and repair of tissues, just to name a few.

All organs and tissues, with the exception of the central nervous system, are able to use the delivered oxygen to the full, that is, 100%. This is also true for the myocardium [15]. In a healthy individual, however, there is a wide safety margin. Oxygen delivery in healthy resting humans exceeds the needs fourfold. The body as a whole uses only about one in four of the hemoglobin’s oxygen molecules. The amount of oxygen used is called oxygen consumption (VO₂). Another way to express the use of oxygen is the oxygen extraction ratio O₂ER. It describes the percentage of oxygen extracted from the hemoglobin molecule. The total body’s normal resting O₂ER equals about 20–25%. But the organ-specific oxygen extraction varies. Kidneys extract only 5–10%, and the heart at rest 55% [4]. It can be seen from such numbers that oxygen delivery is not the only determinant in the body’s oxygen balance. Only the concerted efforts of all systems included in oxygen supply and use make aerobic life possible.

Pathophysiology of anemia

The human body is a marvel of creation. It is equipped with amazing mechanisms to maintain its function and to ensure that its tissue and organ systems tolerate a broad variety of conditions. This is also true for diminished levels of hemoglobin. Oxygen delivery remains sufficient over a wide range of hemoglobin levels, and even when hemoglobin levels have decreased markedly, the body can survive. All this is due to a variety of compensatory mechanisms, some of which are reviewed on the following pages.

The initial adaptation to blood loss is not mainly a reaction to a decrease in oxygen-carrying capacity but rather the body’s reaction to hypovolemia. If left alone, the human body initiates a series of changes: first, to restore blood volume and second, to restore red cell mass. Within minutes, heart rate and stroke volume increase. The adrenergic system and the renin-angiotensin-aldosterone system are stimulated, releasing vasoactive hormones. This leads to the constriction of vascular sphincters in the skin, skeletal muscle, kidneys, and splanchnic viscera. The blood flow is redistributed to high-demand organs, namely the heart and brain [16]. To restore intravascular volume, fluids are first shifted from the interstitial space to the vessels, and later from the intracellular to the extracellular space. Due to adaptations in renal function, water and electrolytes are conserved. The liver is stimulated to produce osmotic active agents (glucose, lactate, urea, phosphate, etc.), which results in a net shift of fluid into the vasculature [16] and thus preload increases. Unless compensatory mechanisms fail, cardiac output is restored within 1–2 minutes [17].

However, if the body’s compensatory mechanisms fail, cardiac output and oxygen delivery decrease. At that point, restoration of blood volume (not red cell volume) is mandatory. If fluids are infused, cardiac output can be increased and the untoward effects of hypovolemia averted.
Blood flow is restored and the body is able to repair damage and replenish the loss of red cell mass.

In the following paragraphs, the trip through the human body is repeated—this time under anemic, yet normovolemic, conditions. The assumption is that the patient is already volume-resuscitated and that adaptive mechanisms are mainly due to reduced red cell mass rather than reduced intravascular volume.

**Adaptation of the body: acute is not the same as chronic**

It is not uncommon to meet persons with a hemoglobin value of less than 4 g/dL doing their normal job—the only clinically observable effect being reduced exercise tolerance. On the other hand, some patients with the same hemoglobin level are hardly capable of lifting their head. Responses to blood loss and anemia are obviously not uniform. How the body responds to anemia depends on the rapidity of blood loss, the underlying condition of the patient, drugs taken, preexisting hemoglobin level, etc. [18]. Some adaptive mechanisms are more pronounced in acute anemia while others are more common in chronic anemia.

**Adaptive mechanisms to anemia: macrocirculation**

Leonardo da Vinci said: “Movement is the cause of all life.” This also holds true for blood loss and anemia. In anemia, increased flow, that is, cardiac output, compensates for the losses in hemoglobin. In the acute setting, cardiac output increases with increasing levels of volume-resuscitated anemia. This is mainly due to increases in stroke volume. The influence of the heart rate in increasing the cardiac output is a subject of debate. Results conflict depending on the animal species studied and the patients and their conditions (anesthetized versus awake, influence of drugs taken). It seems, however, that an increase in the heart rate is not the main determinant in increasing the cardiac output of acutely anemic, volume-resuscitated individuals [18, 19].

Two major mechanisms are responsible for increased cardiac output. The most important is a reduction in blood viscosity. This results in increased venous flow with increased flow to the right heart. Preload increases, resulting in an enhanced cardiac output. Afterload is reduced by the decrease in blood viscosity. The other important cause for the increase in cardiac output is stimulation of the sympathetic nerve system. Via the sympathetic nerve system and a catecholamine release, myocardial contractility (and heart rate) increases, and again, the cardiac output increases.

Both, in acute and chronic anemia cardiac output is increased by means of viscosity reduction and sympathetic nerve stimulation. And if anemia is becoming chronic, the heart adapts to the increased workload with left ventricular hypertrophy.

In the discussion of macrocirculatory adaptations to anemia, special consideration must be given to the heart. The myocardium requires more oxygen than any other organ and has a high O2ER even at rest. When the heart’s oxygen demand increases, e.g., by increased cardiac workload, the heart can slightly increase its oxygen extraction. The major increase in oxygen delivery to the heart, however, is due to vasodilatation of the coronary arteries. Normally, there is a great reserve in myocardial blood flow [20]. However, if myocardial blood flow cannot be increased, the heart may not be able to receive the oxygen it needs for its vital work. On the one hand, increased myocardial work is beneficial to compensate anemia. But then, increased myocardial work increases the heart’s oxygen demand. Since an increase in the cardiac output is a crucial factor in compensating for the loss of oxygen-carrying capacity, it is vital for the heart to be able to increase its output on demand. Several factors can impair the heart’s ability to increase output. Coronary stenosis, myocardial insufficiency, sepsis, anesthetics, and other drugs may compromise the work of the heart [21]. In such situations, the increase in cardiac output may not be sufficient to compensate for the lost red cell mass. Studies show that patients with different pathologies of the heart are more susceptible to ischemia than other patient populations and tolerate anemia less than the same patients without cardiac pathology.

Closely related to anemia-induced changes in cardiac output is the alteration of vascular tone. Again, the sympathetic nerve system plays an important role in this [18]. Increased activity of aortic chemoreceptors has been postulated to change vasomotor tone, and thus afterload [4]. Part of the reduction in afterload may also be due to hypoxic vasodilatation.

An increase in cardiac output and a reduction in vascular tone lead to an increased blood flow. The flow is directed to high-demand organs, with the brain and heart first in line to get a major portion of the blood [22]. Even under normal conditions they extract most of the oxygen offered by the hemoglobin [4] and are therefore supply dependent. Redistribution of the blood flow takes place at the expense of noncritical organs [23], e.g., the skin.
Volume-resuscitated anemic patients have a greater plasma volume than healthy, nonanemic humans. This volume serves to transport physically dissolved oxygen. While the portion of physically dissolved oxygen is almost insignificant in nonanemic patients, it must not be underestimated in severely anemic patients. At times, it may constitute a major portion of the total oxygen delivered by the blood [24].

Another adaptive mechanism of anemia tolerance is increased oxygen extraction. As shown above, given normal conditions, on average only one out of four oxygen molecules carried by a hemoglobin molecule is extracted by the body. Most tissues would be able to extract much more oxygen from the hemoglobin. In fact, in severe states of anemia, most tissues can extract nearly 100% of the oxygen offered. The increase in O2ER is thus a valuable tool to compensate for decreased oxygen carriers.

The extent to which the above-mentioned adaptive mechanisms are being used by the body differs from patient to patient: The degree of anemia as well as the condition of the patient, the comorbidities, and the rapidity of the development of anemia play a role. If anemia becomes a chronic state, systemic vascular resistance returns to normal. Cardiac output is not increased to the same high degree as in acute anemia. Redistribution of blood flow from organs, with excess flow to other organs, takes place [4]. A combination of adaptive mechanisms enable a chronically anemic body to meet oxygen demand, even at times when hemoglobin levels are extremely low.

As a combined effect of reduction of blood viscosity, increase in cardiac output, etc., delivery of oxygen increases as the hematocrit starts to decrease. Oxygen delivery reaches its maximum at a hematocrit of 25–33% [4]. At hematocrits above 45 and below 25, oxygen delivery decreases. Adaptation in cardiac output compensates for decreased oxygen-carrying capacity. This results in an almost constant delivery of oxygen to the capillaries, as long as red cell losses do not exceed about 50% in healthy persons [13].

How do red cells take up oxygen?
Adaptive mechanisms begin again in the lung, the place where red cells exchange gases. Despite a reduction of the blood’s capacity for carrying O2 and CO2, even severe anemia is associated with remarkable stability of the pulmonary gas exchange [25]. Compensatory mechanisms kick in, ensuring that O2 transport and CO2 elimination are not impaired [26].

In anemia, lung perfusion is altered. Less hemoglobin molecules are available for interaction with NO, which preserves the vasodilatory effect of NO. Resistance to pulmonary blood flow is thus decreased [27]. This leads to an increased flow of blood through the pulmonary vasculature. This flow increases the shear stress in the endothelium, thus further increasing the production of vasodilating NO. Those vasodilatory effects counteract hypoxic pulmonary vasoconstriction [25]. In anemia there is a tendency toward reduced heterogenicity of pulmonary blood flow. Selective constriction of pulmonary vessels diverts blood to better ventilated alveoli [28]. NO may also alter airway tone, leading to a redistribution of ventilation. All this results in improved gas exchange in the lung. Several studies showed that arterial partial pressure of oxygen in anemic patients may even be greater than in nonanemic patients.

How do red cells reach their goal, the microvasculature in the tissue?
There is a clear relationship between hematocrit and viscosity. As the hematocrit decreases, blood viscosity decreases and red cells travel at a higher speed. When traveling at this high speed, they do not have sufficient time to lose oxygen on the way to the tissue. Therefore, in anemic conditions red cells arrive in the microcirculation with more oxygen than that in nonanemic conditions [4].

Since FCD is important for tissue survival, several mechanisms are employed in anemia to recruit capillaries. The blood flow in the capillaries of anemic patients is more homogenous than in nonanemic ones [19]. Several mechanisms account for this. Hemoglobin has a very high affinity for NO. This property is a crucial factor for regulating the interaction of red cells and the endothelium. Red cells have the ability to constrict the vascular bed by scavenging the vasodilator NO. This effect is concentration dependent; that is, the lower the hematocrit, the more the vasodilatation and the better tissue perfusion. A better flow of blood in anemic states results. “Physical stimuli such as fluid shear stress, pulsatile stretching of
the vessel wall, or a low arterial $\text{PO}_2$, also stimulate the release of NO above the basal level” [29]. Furthermore, in anemia, red cells do not aggregate readily and are able to pass through the narrowest capillary. Arterial/venular diffusional shunting is diminished because of the increased blood velocity and the decreased red cell residence time in the vessels [13]. While in the acute anemic setting the body is only able to recruit available capillaries, in the chronic anemic setting new vessels develop (neoangiogenesis).

Capillary vessels need arterial pressure to remain open. As blood viscosity decreases in anemia, flow increases because less arterial pressure is lost struggling with high blood viscosity. Thus, the lowered blood viscosity improves capillary perfusion. For this reason hemodilution is used therapeutically to improve tissue oxygenation. However, the beneficial effect of reducing the blood viscosity is only apparent as long as the heart can compensate for lost hemoglobin by improving flow. At the point where the heart can no longer compensate for the red cell loss, this beneficial effect ceases to exist. Hemodilution beyond this point reduces viscosity still further, inducing vasoconstriction and thus reducing FCD. At that point, a therapeutic maneuver may be employed to improve tissue perfusion again. Vessels are dependent on shear stress to open. By artificially increasing blood viscosity, shear stress to the vessels can be exerted, eliciting a vasodilatory response. This may result in recovery of FCD [8, 13, 30].

In a summary of some interesting findings about the relationship of blood viscosity and transfusions the author stated: “Microcirculatory studies show that the organism compensates for reduced blood viscosity only up to reductions coincident with the conventional transfusion trigger and that reductions beyond this point lower functional capillary density. These studies show that the critical limit for tissue survival at the transfusion trigger is functional capillary density. Functional capillary density is important, primarily, for the extraction of tissue metabolism byproducts and, secondly, for tissue oxygenation. Thus, the transfusion trigger signals a condition where the circulation no longer compensates for significantly lowered viscosity due to hemodilution. Continued hemodilution with high-viscosity plasma expanders beyond the transfusion trigger is shown to maintain functional capillary density and improve tissue perfusion, suggesting that the conventional transfusion trigger is a viscosity trigger . . . ” [31]. And after a discussion of the benefits of higher blood viscosity after reaching the “transfusion trigger,” the author concluded: “It is a corollary to these considerations that the level of oxygen carrying capacity required to safely oxygenate the tissue may be much lower than that dictated by medical experience if microvascular function is maintained” [13].

**How do the red cells give oxygen and how does the tissue take up oxygen?**

In states of anemia, the oxygen affinity of hemoglobin is lowered as is reflected in a right shift in the oxygen dissociation curve. This facilitates oxygen release to the tissue. The right shift in the oxyhemoglobin dissociation curve is the result of increases of 2,3-DPG in red cells [18]. In contrast to chronic anemia, however, facilitated $O_2$ dissociation does not play too big a role in acute anemia where 2,3-DPG levels do not change significantly [20]. Theoretically, in anemia also a shift in pH toward greater acidity may enhance oxygen release (Bohr effect). However, this effect is probably not clinically relevant since immense changes in pH are needed to release significant amounts of oxygen from red cells [18].

Reserves in oxygen delivery are used in anemia, and this is reflected in an increased oxygen extraction ratio. Normally, the tissue extracts only about 20–30% of the total oxygen delivered. In anemia, the tissue may extract much more so that body $O_2$ER as a whole increases to 50–60%. As a consequence, the mixed venous oxygen partial pressure decreases.

In extreme anemia, oxygen uptake by the tissue seems to be limited. This may be due to the increased flow and the decreased transit time of red cells in the microvasculature. Time available for oxygen diffusion may be insufficient [32]. Also, erythrocyte spacing (increased distance between adjacent red cells during anemia) and the diffusion distance may contribute to this phenomenon [33].

**Does the tissue use oxygen?**

The last stop on this trip through the anemic body is again the tissue with the mitochondria, the place where a decrease in oxygen delivery should matter most. Intracellular mechanisms sense the decrease of $O_2$ in the tissue. In response, hypoxia-dependent gene expression is stimulated. A key factor in this process is the hypoxia-inducible factor $\alpha$ (HIF1$\alpha$). It “induces the expression of genes that influence angiogenesis and vasodilatation, erythropoiesis and increased breathing, as well as glycolytic enzyme genes for anaerobic metabolism” [34]. Interestingly, the basic
mechanisms of hypoxia tolerance are shared by different species, including humans. The following model was described for animals.

So, what happens if a cell senses a decrease in oxygen supply? Does the cell die? Not right away. The cell needs oxygen mainly to produce energy (ATP). So it makes sense that in anticipation of reduced oxygen (that is, energy) supply, energy demand is reduced. What does a cell need energy from ATP for? Almost all energy is needed for protein synthesis and degradation, maintenance of ion gradients, and synthesis of glucose and urea. And, in fact, in an initial defense phase, cells greatly (>90%) and rapidly suppress their protein, glucose, and urea synthesis. Interestingly, ion gradients over membranes remain constant, although the pumping activity of ion pumps is reduced to save energy. The cells use different mechanisms to accomplish this miracle. For instance, liver cells reduce cell membrane permeability, a process called channel arrest. Nerve cells reduce the firing frequency (spike arrest). Employing such measures, many cells can attain an energy balance at a lower level (ATP demand = ATP supply). This may ensure long-term survival in hypoxia. Hypoxia-sensitive cells, however, do not attain a new balance.

After the defense phase, a second, “rescue” phase, follows. Cells are now aiming at long-term hypoxia survival. To that end, cells reactivate some protein biosynthesis to prepare the cell for survival with extremely low ATP turnover. Hypoxia-dependent expression of key factors (such as HIF 1) regulates this process. Housekeeping genes consolidate and stabilize the cell, and enzymes for anaerobic ATP production are upregulated [34, 35]. With changes like these, cells can function for a while with a very low oxygen delivery.

### Relationship between oxygen delivery and oxygen consumption

As mentioned initially, the aim of anemia therapy is to match the tissue’s demand for oxygen with supply. This demand is reflected by tissue oxygen consumption VO₂. There is a relationship between oxygen delivery and oxygen consumption (Fig. 2.2). Oxygen consumption remains constant over a wide range of delivery. At the point where oxygen consumption becomes supply dependent, tissue hypoxia may occur. This point is called “critical oxygen delivery,” DO₂crit. This, however, is no fixed number, leaving room for therapeutic interventions.

![Fig 2.2 Relationship between oxygen delivery and oxygen consumption. Continuous line: healthy individuals; dashed line: pathologic as in severe illness (with a wider range of dependence of VO₂ on DO₂ and a higher DO₂crit).](image)

### Practical implications

The oxygen delivery equation \([\text{DO}_2 = \text{CO} \times (\text{Hgb} \times 1.34 \times \text{SaO}_2 + 0.003 \times \text{PaO}_2) \times 10]\) may serve as a mnemonic for available anemia treatments. Every variable in the equation can be considered, based on which therapeutic interventions can be evaluated to optimize oxygen delivery. The cardiac output can be optimized by administering balanced amounts of intravenous fluids and removing negative inotropic influences or increasing positive inotropics as tolerated. The hemoglobin level can be increased, not only by speeding up endogenous hematopoiesis, but also by avoiding undue hemoglobin losses. Arterial oxygen partial pressure and oxygen saturation can be increased, using supplemental oxygen and mechanical ventilation as indicated. In addition, the amount of oxygen dissolved in plasma can be increased further by increasing the atmospheric pressure (hyperbaric oxygen).

A more complete picture of anemia therapy, though, is achieved when not only an increase of oxygen delivery is aimed at, but also a reduction of oxygen demand is contemplated. Oxygen delivery and consumption are related, since \(\text{VO}_2 = \text{DO}_2 \times \text{O}_2\text{ER}\). While not many interventions are available to increase oxygen extraction, there are quite a few things that can be done to reduce oxygen consumption. “The four pillars of anemia therapy” (Fig. 2.3) summarize how an understanding of physiology and pathophysiology translates into a plan of care. With the appropriate combination of factors that not only increase oxygen delivery but also reduce oxygen consumption, even hemoglobin levels way below the supposed
The four pillars of anemia therapy

<table>
<thead>
<tr>
<th>Minimize bloodloss</th>
<th>Optimize O₂-delivery</th>
<th>Reduce oxygen need</th>
<th>Enhance hematopoiesis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stop bleeding</td>
<td>Volume therapy</td>
<td>Manage pain</td>
<td>Prescribe vitamins B + C, folate, iron</td>
</tr>
<tr>
<td>Minimize phlebotomy</td>
<td>Increase inspired oxygen fraction</td>
<td>Sedate</td>
<td>Administer erythropoietin or anabolics</td>
</tr>
<tr>
<td>Provide ulcus prophylaxis</td>
<td>Treat thoracic injuries</td>
<td>Intubate, ventilate, relax</td>
<td>Avoid marrow depressants</td>
</tr>
<tr>
<td>Avoid hemolytic drugs</td>
<td>Optimize ventilation</td>
<td>Give antioxidants</td>
<td>Consider other growth factors (CSF)</td>
</tr>
<tr>
<td>Normalize clotting</td>
<td>Intubate</td>
<td>Maintain normothermia</td>
<td>Pay attention to appropriate nutrition</td>
</tr>
<tr>
<td>Give contraceptives</td>
<td>Give hyperbaric oxygen</td>
<td>Consider β-blockade</td>
<td></td>
</tr>
<tr>
<td>Avoid hypertension and hypervolemia</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Fig 2.3 The four pillars of anemia therapy.

critical border can be tolerated for some time without lasting damage [36], and even severely anemic patients can be treated successfully.

Key points

- Many mechanisms are used by the body to survive even severe anemia; these include the following:
  - increased cardiac output
  - redistribution of blood flow to organs with high oxygen demand
  - increased oxygen extraction by tissues
  - improved FCD
  - decreased oxygen affinity of hemoglobin
  - metabolic adaptations to tolerate lower oxygen delivery.
- Therapeutic interventions are aimed at finding a new balance between oxygen delivery and oxygen consumption, either by increasing oxygen delivery or by reducing oxygen consumption or both at the same time.

Questions for review

- What mechanisms support red cell oxygen uptake and oxygen release?
- Where is oxygen release from the red cells to the tissue regulated?
- What does the term functional capillary density mean? How can it be influenced?
- How do cells prepare when decreasing oxygen levels are detected?
- How is blood flow altered in anemic states?
- How do adaptation methods for acute and chronic anemia differ?

Suggestions for further research

What different forms of hypoxia are there and how do they differ?