Microcirculatory Effects of Hemoglobin Solutions
Progress in Applied Microcirculation

Vol. 25

Series Editor

K. Messmer Munich
Microcirculatory Effects of Hemoglobin Solutions

Volume Editors

K. Messmer  Munich
K.E. Burhop  Deerfield, Ill.
J. Hutter   La Jolla, Calif.

31 figures, 6 in color, and 9 tables, 2004
Contents

VII List of Participants

IX Preface

1 Shear Stress Effects on Endothelial Cells
   Frangos, J.A.; White, C.R.; Intaglietta, M. (La Jolla, Calif.)

8 Microvascular Transport Factors in the Design of Effective Blood Substitutes
   Intaglietta, M. (La Jolla, Calif.)

16 Tissue Oxygen Effects of HBOC-201 versus Red Blood Cells
   Jacobs, Jr., E.E.; Gawryl, M.S. (Cambridge, Mass.)

27 Dextran-Conjugated Hemoglobin Does Not Alter Microcirculatory Parameters after Moderate Hemodilution
   Caron, A.; Hutter, J. (Munich); Menu, P. (Nancy); Messmer, K. (Munich)

39 Total Blood Exchange with Diaspirin Cross-Linked Hemoglobin Is Compatible with Long-Term Survival
   Hutter, J.; Sinitsina, I.; Hermann, J.; Messmer, K. (Munich)

48 The Development and Preclinical Testing of a Second-Generation Recombinant Hemoglobin Solution, rHb2.0 for Injection
   Burhop, K.E.; Doyle, M.P. (Boulder, Colo.)

65 Moderate Hemodilution with rHb2.0 for Injection
   Hutter, J.; Hermann, J.; Juri, G.; Messmer, K. (Munich)
75 rHb2.0 for Injection for Resuscitation from Hemorrhagic Shock
Hermann, J.; Hutter, J.; Messmer, K. (Munich)

86 Influence of Hemoglobin-Based Oxygen Carriers with Different Nitric Oxide Scavenging Properties on the Pancreatic Microcirculation after Hemorrhagic Shock
von Dobschuetz, E. (Freiburg); Hutter, J.; Hoffmann, T.; Messmer, K. (Munich)

95 Background and Initial Preclinical Results with a Novel Second-Generation Blood Substitute
Proctor, K.G.; Cohn, S.M. (Miami, Fla.)

103 Author Index
104 Subject Index
List of Participants

Burhop, K.E., PhD, Baxter Healthcare Corporation, Hemoglobin Therapeutics Program, 2545 Central Avenue, Boulder, CO 80301 (USA)
Caron, A., PhD, Aventis Pharma, Gencell SA, 72–82, rue Leon Geoffroy, FR–94400 Vitry-sur-Seine (France)
Chávez Negrete, A., MD, PhD, Clinic Research Unit, Cardiology Hospital, Instituto Mexicano del Seguro Social, Av. Cuauhtemoc 330, Col. Doctores, 06720 Mexico DF (Mexico)
Doyle, M., PhD, Baxter Healthcare Corporation, Hemoglobin Therapeutics Program, 2545 Central Avenue, Boulder, CO 80301 (USA)
Frangos, J.A., PhD, La Jolla Bioengineering Institute, 505 Coast Boulevard South, La Jolla, CA 92037 (USA)
Frey, L., Dr., Klinik für Anästhesiologie, Ludwig-Maximilians-Universität, Klinikum Grosshadern, Marchioninistrasse 15, DE–81377 München (Germany)
Gaehtgens, P., Prof. Dr., Physiologisches Institut der Freien Universität Berlin, Arnimallee 22, DE–14195 Berlin (Germany)
Gawryl, M., PhD, Biopure Corporation, 11 Hurley Street, Cambridge, MA 02141 (USA)
Habler, O., PD Dr., Klinik für Anästhesiologie, Ludwig-Maximilians-Universität, Klinikum Grosshadern, Marchioninistrasse 15, DE–81377 München (Germany)
Hermann, J., Institut für Chirurgische Forschung, Ludwig-Maximilians-Universität, Klinikum Grosshadern, Marchioninistrasse 15, DE–81377 München (Germany)
Högl, S., Institut für Chirurgische Forschung, Ludwig-Maximilians-Universität, Klinikum Grosshadern, Marchioninistrasse 15, DE–81377 München (Germany)
Hutter, J., Dr., Institut für Chirurgische Forschung, Ludwig-Maximilians-Universität, Klinikum Grosshadern, Marchioninistrasse 15, DE–81377 München (Germany)
Intaglietta, M., PhD, MD (Hon), Department of Bioengineering, University of California, San Diego, 9500 Gilman Drive, La Jolla, CA 92093 (USA)
Jacobs, E., MD, 29 Concord Avenue, Cambridge, MA 02138 (USA)
Kemming, G., Dr., Klinik für Anästhesiologie, Ludwig-Maximilians-Universität, Klinikum Grosshadern, Marchioninistrasse 15, DE–81377 München (Germany)
Krombach, F., Prof. Dr., Institut für Chirurgische Forschung, Ludwig-Maximilians-Universität, Klinikum Grosshadern, Marchioninistrasse 15, DE–81377 München (Germany)
Meier, J., Institut für Chirurgische Forschung, Ludwig-Maximilians-Universität, Klinikum Grosshadern, Marchioninistrasse 15, DE–81377 München (Germany)
Meisner, F., Dr., Abteilung für Thorax- und Gefässchirurgie, Chirurgische Universitäts- und Poliklinik, Universität Ulm, Steinhövelstrasse 9, DE–89075 Ulm (Germany)
Mempel, W., Prof. Dr., Abteilung für Transfusionsmedizin, Medizinische Klinik III, Klinikum Grosshadern, Ludwig-Maximilians-Universität, Marchioninistrasse 15, DE–81377 München (Germany)
Menu, P., PhD, Faculté de Pharmacie de Nancy, Université Henri Poincaré, 5, rue Albert Lebrun, FR–54001 Nancy Cedex (France)
Mercuriali, F., Prof. Dr., Ospedale Niguarda Ca’Granda, Piazza Ospedaletto Maggiore 3, IT–20162 Milano (Italy)
Messmer, K., Prof. Dr., Dr. h.c.mult., Institut für Chirurgische Forschung, Ludwig-Maximilians-Universität, Klinikum Grosshadern, Marchioninistrasse 15, DE–81377 München (Germany)
Proctor, K.G., PhD, Daughtry Family Department of Surgery, Ryder Trauma Center, School of Medicine, University of Miami, 1611 NW 12th Avenue, Miami, FL 33136 (USA)
Raat, H., Academic Medical Center, University of Amsterdam, Meibergdreef 9, NL–1105 AZ Amsterdam (The Netherlands)
Tsai, A., PhD, Department of Bioengineering, University of California, San Diego, 9500 Gilman Drive, La Jolla, CA 92093 (USA)
van Iterson, M., MD, Department of Anesthesiology, Academic Medical Center, University of Amsterdam, Meibergdreef 9, NL–1105 AZ Amsterdam (The Netherlands)
von Dobschütz, E., Dr., Abteilung für Allgemein- und Viszeralchirurgie, Chirurgische Universitätsklinik, Albert-Ludwigs-Universität, Hugstetter Strasse 55, DE–79106 Freiburg (Germany)
Preface

The last Bodensee Symposium on Microcirculation held in June 2002 was dedicated to the topic of the effects of hemoglobin solutions on the microcirculation.

Hemoglobin solutions have been investigated for their potential as blood substitutes for more than 70 years. Recently a shift in paradigm has taken place based on the notion that the function of hemoglobin, namely of picking up oxygen in the lung, transporting it to the microcirculation and unloading it at the tissue level is not necessarily connected with just volume replacement properties. Restitution of blood or plasma volume can be effectively achieved by means of colloidal solutions. If resuscitation of microcirculatory function is the critical issue, hypertonic-hyperoncotic solutions offer an effective substitute, as extensively discussed in volume 22 of this series entitled Compromised Perfusion.

Hemoglobin-based resuscitation solutions have presented with many unwanted side effects, in particular renal toxicity and hypertension. Over the last decades many of these side effects have been reduced or eliminated by producing new formulations utilizing chemical and/or recombinant approaches to avoid the dissociation of the tetrameric molecule into dimers. Inter- and intramolecular linking of stroma-free hemoglobin of bovine or human (recombinant-derived or from outdated RBCs) origin has essentially eliminated the renal problem, while other procedures have yielded hemoglobin molecules with the desired affinity for oxygen. During the last years it has become apparent that the long-known vasoconstrictive effect of hemoglobin carried in the plasma compromises the microvascular perfusion of organs where oxygen unloading should take place at the tissue level. One of the prevailing assumptions is that the high
affinity of free hemoglobin for nitric oxide results in precapillary vasoconstriction, and thus tissue underperfusion and prevention of tissue oxygenation. A number of new recombinant approaches that involve site-directed mutagenesis, as well as some chemical approaches involving polymerization and pegylation, have been developed to resolve this critical issue. Therefore the symposium was devoted to the discussion of the microcirculatory effects of the hemoglobin solutions presently under scrutiny and researchers working with different compounds were invited to the Bodensee.

This volume gives a first overview on the effects of different hemoglobin solutions on the microvasculature and tissue oxygenation, independently of the potential of the compounds soon to enter the clinical field.

We are indebted to the sponsor of the Symposium, The Hemoglobin Therapeutics Division of the Baxter Healthcare Corporation, Boulder, Colo., USA. The symposium participants once again enjoyed the hospitality of Hotel Bad Schachen and its proprietors, Family Schielin. Finally we would like to thank the staff of S. Karger AG Basel for the production of these proceedings and Mr. Werner Dresel, Incoma GmbH, Heusenstamm, Germany for his help in the organization of this symposium.

K. Messmer
K.E. Burhop
J. Hutter