
**FIRST VIENNA
SHOCK FORUM**
Part A: Pathophysiological
Role of Mediators and
Mediator Inhibitors in Shock

Proceedings of the First Vienna Shock Forum held May 1-3, 1986

Editors

Günther Schlag
Heinz Redl

Ludwig Boltzmann Institute
for Experimental Traumatology
Vienna, Austria

ALAN R. LISS, INC. • NEW YORK

**Address all Inquiries to the Publisher
Alan R. Liss, Inc., 41 East 11th Street, New York, NY 10003**

Copyright © 1987 Alan R. Liss, Inc.

Printed in the United States of America

Under the conditions stated below the owner of copyright for this book hereby grants permission to users to make photocopy reproductions of any part or all of its contents for personal or internal organizational use, or for personal or internal use of specific clients. This consent is given on the condition that the copier pay the stated per-copy fee through the Copyright Clearance Center, Incorporated, 27 Congress Street, Salem, MA 01970, as listed in the most current issue of "Permissions to Photocopy" (Publisher's Fee List, distributed by CCC, Inc.), for copying beyond that permitted by sections 107 or 108 of the US Copyright Law. This consent does not extend to other kinds of copying, such as copying for general distribution, for advertising or promotional purposes, for creating new collective works, or for resale.

Library of Congress Cataloging-in-Publication Data

Vienna Shock Forum (1st : 1986)
First Vienna Shock Forum.

(Progress in clinical and biological research ; 236)

Contents: pt. A. Pathophysiological role of mediators and mediator inhibitors in shock—pt. B. Monitoring and treatment of shock.

Includes bibliographies and index.

I. Shock—Congresses. I. Schlag, Günther.

II. Redl, Heinz. III. Title. IV. Series: Progress in clinical and biological research ; v. 236. [DNLM: 1. Monitoring, Physiologic—congresses. 2. Shock—physiopathology—congresses. 3. Shock—therapy—congresses.

W1 PR668E v.236 / QZ 140 V662 1987f]

RB150.S5V54 1987 616'.047 87-3921

ISBN 0-8451-5086-3 (set)

ISBN 0-8451-0196-X (pt. A)

ISBN 0-8451-0197-8 (pt. B)



Contents

Contributors	xiii
Contents of Part B	xxiii
Preface	
Günther Schlag and Heinz Redl	xxv
 1. THE PATHOPHYSIOLOGICAL ROLE OF MEDIATORS AND INHIBITORS THEREOF IN SHOCK	
 1.1. Complement—Granulocytes	
Complement Activity in Shock	
Mats Heideman and Anders Bengtson	3
Inflammatory Mediators in Patients With Ischemic Limbs	
Anders Bengtson, Pia Holmberg, and Mats Heideman	11
Granulocytes as Mediators of Tissue Injury in Shock: Therapeutic Implications	
Dale E. Hammerschmidt and Gregory M. Vercellotti	19
Role of Fibrin-Neutrophil Interactions in Lung Vascular Injury	
Asrar B. Malik	33
Quantitative Estimation of Leukostasis in the Posttraumatic Lung—Canine and Human Autopsy Data	
Heinz Redl, Hans P. Dinges, and Günther Schlag	43
Whole Body Inflammation in Trauma Patients; an Autopsy Study	
Hans K. S. Nuytinck, Xavier J.M.W. Offermans, Karel Kubat, and R. Jan A. Goris	55
White Cells in Shock Ischemia	
David H. Lewis, Anders Gidlöf, Kristina E-dr. Behm, Maj-Britt Bengtsson, and Angela Menschik	63
Neutrophil Protease Enzymes and Oxygen Free Radicals as Mediators of Pulmonary Membrane Damage	
Stephen Westaby	75
 1.2. Proteases	
Studies on Shock During Extracorporeal Circulation During Aorto-Coronary Bypass Operations	
Wolfgang Heller, Günther Fuhrer, Hans-Eberhard Hoffmeister, and Michael J. Gallimore	87

Biochemical Monitoring of the Lung During and After Extracorporeal Circulation	
Geza Horpacsy, Werner Hügel, Hugo Müller, and Alfred Geißler	95
Effect of Elevated C1-Esterase Inhibitor Levels on Elastase Release In Vitro—A Proposed Model of Shock (ECC)	
Wolfgang Heller, Günther Fuhrer, Susanne Hoberg, Hans-Eberhard Hoffmeister, and Anton Philipitsch	107
Granulocyte Elastase and White Cell Counts in Septic Pigs	
M. Siebeck, H. Hoffmann, and R. Geiger	115
Influence of the Lysosomal Elastase Inhibitor Eglin on the Development of Interstitial Lung Edema in <i>E. coli</i> Bacteremia in Pigs	
H.F. Welter, M. Siebeck, O. Thetter, and M. Jochum	121
Evaluation of the Kinin-Induced Pathomechanisms in the Development of ARDS by Kallikrein Inhibition In Vivo	
O. Thetter, H. Hoffmann, M. Siebeck, H.F. Welter, and H. Fritz	127
Local Activation of the Kallikrein-Kinin System in the Lung Following <i>E. coli</i> Sepsis in Sheep	
Svenerik Andreasson, Lennart Smith, Ansgar O. Aasen, and Bo Risberg	133
C1-Esterase Inhibitor in Early Septicemia	
M. Siebeck, A. Philipitsch, H. Wiesinger, and H.F. Welter	141
Anti-Proteases in Endotoxemia	
Daniel L. Traber	149
Effect of Aprotinin and C1-Esterase Inhibitor on Activation of the Plasma Kallikrein-Kinin System In Vivo	
H. Hoffmann, M. Siebeck, O. Thetter, E. Fink, and A. Philipitsch	159
Cellular Effects of Aprotinin	
Heinz Redl, Anna Schiesser, Eva Paul, Claudia Wilfing, and Günther Schlag	165
Feasibility Study of Very High Aprotinin Dosage in Polytrauma Patients	
C. Clasen, M. Jochum, and W. Mueller-Esterl	175
Hemodynamics and Proteolysis in Experimental Trypsin Induced Shock	
Froye Naess, Johan Pillgram-Larsen, Tom E. Ruud, Jan O. Stadaas, and Ansgar O. Aasen	185
Protease Inhibitor Infusion Improves Survival Rate and Hemodynamics in Experimental Pancreatic Shock	
Tom E. Ruud, Ansgar O. Aasen, Johan Pillgram-Larsen, and Jan O. Stadaas	193
Biologic Availability of Injected or Aerosolized Alpha₁ Proteinase Inhibitor	
R.M. Smith, R.G. Spragg, and K.M. Moser	203
Multitherapy: A New Treatment Regimen in Endotoxemia	
Ansgar O. Aasen, Tom E. Ruud, Johan Pillgram-Larsen, and Jan O. Stadaas	211
Hemodynamic Consequences of Multitherapy Pretreatment in Experimental Endotoxemia	
J. Pillgram-Larsen, T.E. Ruud, J.O. Stadaas, and A.O. Aasen	227

1.3 Oxygen Radicals—Lipid Peroxidation**Oxygen Radicals and Lipid Peroxidation in Experimental Shock**

Gerd O. Till and Peter A. Ward 235

Cytotoxic Lipid Peroxidation ProductsHermann Esterbauer, Ernst Koller, Peter Heckenast, Robert Moser,
and Claude Celotto 245**Oxidant Injury of Cultured Cells: Biochemical Consequences**R.G. Spragg, I.U. Schraufstatter, P.A. Hyslop, D.B. Hinshaw, and
C.G. Cochrane 253**Oxygen Radicals Scavenging in Prophylaxis and Treatment of Experimental Shock**

G.P. Novelli, P. Angiolini, G. Martini, and R. Tani 259

Antioxidant Drugs and Shock Therapy

O. Ortolani, M. Biasiucci, A. Trebbi, M. Cianciulli, and R. Cuocolo 271

Protection by Ebselen Against Endotoxin Shock in Rats or Mice Sensitized by Galactosamine

K.-H. Konz, G. Tiegs, and A. Wendel 281

1.4. Prostaglandins, Leukotrienes, and Platelet Activation Factor**Activation of the Pulmonary Arachidonic Acid System and Its Consequences for Hemodynamics and Fluid Balance**

Heinz Neuhof, Werner Seeger, and Norbert Suttorp 289

Leukotrienes as Mediators in Endotoxin Shock and Tissue Trauma

Dietrich Keppler, Wolfgang Hagmann, and Claudio Denzlinger 301

Generation of Leukotrienes in Polytraumatic Patients With Adult Respiratory Distress Syndrome (ARDS)

J. Knöller, W. Schönfeld, T. Joka, J. Sturm, and W. König 311

On the Pathogenesis of Adult Respiratory Distress Syndrome—The Role of Anaphylatoxins, Leukotrienes and Platelet Activating Factor

U. Pison, K.P. Schmit-Neuerburg, and W. König 317

Increased Hemodynamic and Survival With Endotoxin and Septic Shock With Ibuprofen Treatment

Roger C. Bone, Elizabeth Rogers Jacobs, and Frank J. Wilson, Jr. 327

Effect of Ibuprofen on Components of an Acute Systemic Inflammatory Response Evoked by Intravenous Endotoxin Administration in the Conscious Sheep

Gary J. Jesmok, Frederick Aono, Janet Simpson, and Julian Borgia 333

Effect of the Nonsteroidal Antiinflammatory Agent BW755C in Rat and Sheep EndotoxemiaSoheyl Bahrami, Fred Mihm, Martin Thurnher, Christa Vogl, Anna Schiesser,
Heinz Redl, and Günther Schlag 347

Effectiveness of Prostaglandin E₁ in Adult Respiratory Distress Syndrome William C. Shoemaker	361
Efficiency of Prostacyclin in Rabbit Endotoxin Shock Heinrich Ditter, Peter Röttger, Reinhard Voss, and F. Reinhard Matthias	369
1.5 Endotoxin	
Endotoxin: The Causative Factor of Mediator Release During Sepsis Daniel L. Traber	377
Endotoxin Shock Model in the Dog: A Reevaluation Jean-Louis Vincent, Marc Domb, Pascal Luybaert, Corinne De Boelpaepe, Philippe Van der Linden, and Serge Blécic	393
Perturbation of Transmembrane Signaling Mechanisms in Acute and Chronic Endotoxemia Judy A. Spitzer, Elena R. Turco, Ion V. Deaciuc, and Bryan L. Roth	401
Endotoxin-Induced Generation of Oxygen Free Radicals in Freshly Drawn Human Blood Hubert Reichle, Dagmar Langner, Peter Wendt, and Günther Blümel	419
Inhibition of Lipopolysaccharide-Mediated Activation of Neutrophils With Monosaccharide Derivatives of Lipid A Charles Lam, Elizabeth Basalka, Eberhard Schütze, and Hubert Walzl	427
2. RESULTS OF MEDIATOR RELEASE	
Physiologic and Metabolic Correlations in Human Septic Shock John H. Siegel	439
Multisystem Organ Failure Hans-Peter Schuster	459
Changes in Metabolic Control in Injury and Sepsis Rod A. Little and Keith N. Frayn	463
Catecholamines in the Serum of Multiple Trauma Patients—Mediators of ARDS? P. Sefrin	477
Increased Systemic Microvascular Permeability in Septic Shock A.B. Johan Groeneveld and Lambertus G. Thijs	487
Differences in Regional Oxygen Supply, Oxygen Consumption and Blood Flow During the Onset of E. coli Sepsis G.I.J.M. Beerhuizen, R.J.A. Goris, H.J.M. Beijer, and G.A. Charbon	495
Vascular Perfusion of the Ischemic Small Intestine Miklós Juhász, János Hamar, László Dézsi, Erzsébet Fehér, and Joachim Lutz	503
Reaction Pattern of Alveolar Cells in the Posttraumatic Lung Failure Theo Joka, Udo Obertacke, Wolfgang Schönfeld, Susanne Oberste-Beulmann, Ulrich Pison, Ernst Kreuzfelder, Marianne Jochum, and Gerda Zilow	509

Phospholipid Lung Profile in Adult Respiratory Distress Syndrome— Evidence for Surfactant Abnormality	
U. Pison, E. Gono, T. Joka, and U. Obertacke	517
Wound Inflammatory Mediators and Multisystem Organ Failure	
Robert H. Demling	525
Burn Shock and Its Resuscitation	
David N. Herndon, James G. Hilton, Daniel L. Traber, and Robert E. Barrow .	539
3. THE HEART AS A SPECIAL TARGET ORGAN IN SHOCK	
Evaluation of Heart Performance With Special Emphasis on Severe Hemodynamic Changes During Hypovolemic-Traumatic Shock	
Peter Krösl and Günther Schlag	561
Myocardial Dysfunction in Sepsis	
John J. Spitzer, Lani W. Smith, Edmund C. Burke, and Kathleen H. McDonough	573
Studies on Low Molecular Weight Inotropic Plasma Substances in Prolonged Hypovolemic Traumatic Shock	
Seth Hallström, Christa Vogl, Peter Krösl, Heinz Redl, and Günther Schlag . .	591
Cardiodepressant and Cardiotimulant Factors in Shock	
Sandor Nagy	599
Release of Myocardial Depressant Factor (MDF) During Cardiopulmonary Bypass (CPB): Influence of Corticosteroids (Methylprednisolone) and Protease Inhibitor (Aprotinin)	
Farag I. Coraim, Günther Laufer, Wilfried Ilias, Gregor Wollenek, and Ernst Wolner	611
Endogenous Nickel Release in Injured Patients: A Possible Cause of Myocardial Damage	
Kornél Szabó, István Balogh, and Anna Gergely	621
Heart Rate During Hypotensive Central Hypovolemia Before and After Atropine in Man	
Kåre Sander-Jensen, Jesper Mehlsen, Carsten Stadeager, Peter Bie, and Jørgen Warberg	629
Antioxidant Protection Against Free Radicals Mediated Myocardial Injury	
Elizabeth Röth, Bela Török, William Bär, and Susan Pollak	633
Index	641

Contents of Part B: Monitoring and Treatment of Shock

1. MONITORING OF SHOCK

1.1. Prognostic Indices and Scoring

Scoring Systems and Predictors of ARDS and MOF / R. Jan A. Goris, Hans K.S. Nuytincx, and Heinz Redl

The Use of Scoring Systems as Prognostic Parameter After Surgery and Trauma / Peter Lehmkuhl, M. Ludwig, and I. Pichlmayr

Prediction of Outcome in Sepsis / H.B. Stoner

Prognostic Indices in Septic Shock / Jesús Villar, Miguel A. Blazquez, José A. Bolaños, Juan J. Manzano, and José Quintana

1.2. Biochemical Parameters

Quantification of Granulocyte Enzymes/Proteins With Immunoassays / H. Lang, S. Neumann, W. Rautenberg, H. Fritz, Marianne Jochum, and D. Inthorn

Studies of Granulocyte Function (Chemiluminescence Response) in Postoperative Infection / Dietrich Inthorn, Thomas Szczeponik, Dieter Mühlbayer, Marianne Jochum, and Heinz Redl

Elevated D-erythro-Neopterin Levels in Intensive Care Patients With Septic Complications / Wolfgang Strohmaier, Heinz Redl, Günther Schlag, and Dietrich Inthorn

The Influence of Septic Shock on Plasma Proteins, Lymphocytes and Metabolic Parameters / Erich Roth, Rudolf Steininger, Ingrid Schindler, Gerhard Hamilton, Walter Mauritz, Friedrich Zekert, Manfred Mattausch, Eva Schönthal, Paul Sporn, and Josef Funovics

Inhibition of Beta-FXIIa in Plasma of Volunteers and Polytraumatized Patients / Günther Fuhrer, Michael J. Gallimore, Wolfgang Heller, and Hans-Eberhard Hoffmeister

Can the Outcome After Trauma of Sepsis be Predicted From Biochemical or Hormonal Parameters? / Thomas Pasch, Jörg Mahlstedt, Josef Pichl, Gernot Buheitel, and Edgar Pscheidt

The Proenzyme Functional Inhibition Index as a Predictor in Septicemia / Ansgar O. Aasen

1.3. Hemodynamic Parameters

Physiologic Monitoring and Therapy of High Risk Surgical Patients / William C. Shoemaker

Hämodynamic Pattern in Septic Peritonitis / Heinz Köhler, W. Reichow, J. Martell, G. Köveker, and A. Schafmayer

Early Metabolic and Vascular Tone Patterns in Lethal Sepsis / Ivo Giovannini, Giuseppe Boldrini, Carlo Chiarla, Marco Castagneto, and Giancarlo Castiglioni

Judgement of Central Haemodynamics With and Without Swan Ganz Catheter in Septic Shock States / Gerhard Redl, Ernst Zadrobilek, Ingrid Schindler, Walter Mauritz, and Paul Sporn

Hemodynamic Characterization of Sepsis / K. Lenz, A. Laggner, W. Druml, G. Graninger, G. Grimm, and B. Schneeweiß

1.4. Extravascular Lung Water

Intravascular Starling Forces and Extravascular Lung Water in Advanced Septic Shock States / Ernst Zadrobilek, Ingrid Schindler, Gerhard Redl, Walter Mauritz, Hermann Gilly, Paul Sporn, and Karl Steinbereithner

Dynamics of Extravascular Lung Water in Major Burns / Anton N. Laggner, Kurt Lenz, Gernot Sommer, Wilfried Druml, Bruno Schneeweisz, Georg Grimm, and Gunter Kleinberger

Extravascular Lung Water and Pulmonary Artery Pressure With Acute Respiratory Failure—Effect of Ketanserin Administration / W. Heinrichs, U. Fauth, and M. Halmágyi

2. TREATMENT OF SHOCK

2.1. Basic Supportive Therapy

Prevention of ARDS and MOF by Prophylactic Mechanical Ventilation and Early Fracture Stabilisation / R.J.A. Goris

Modern Strategies of Ventilatory Management in Shock / H. Benzer, M. Baum, J. Koller, W. Koller, G. Kroesen, and N. Mutz

Therapeutic Approaches: Haemodynamic and Respiratory Complications in Septic Shock / P. Lawin, H.J. Lübbesmeier, M. Möllmann, N. Mertes, and H. Van Aken

2.2. Volume Replacement

Fluid Resuscitation in Canine Traumatic-Hemorrhagic Shock: Long-Term Comparison of Hydroxyethyl Starch vs. Ringer's Lactate / Uwe B. Brückner, Michael Albrecht, Lorenz Frey, and Lars-G. Hein

Treatment of Experimental Mesenteric Shock by Different Fluids / János Hamar, Joachim Lutz, László Dézsi, and Miklós Juhász

Does Isovolemic Hemodilution Predispose to Infection? / Wolfgang Graninger, Franz X. Lackner, Reswan Khosropour, Christine Hlozaneck, and Robert Kurz

2.3. Plasmapheresis and Hemofiltration

Plasma Exchange in Septic Shock / Lars J. Bjertnaes

Continuous Pump Driven Hemofiltration (CPDHF) in Septic Renal Failure / Paul Sporn, Walter Mauritz, Gerhard Redl, Ingrid Schindler, Karl Steinbereithner, and Ernst Zadrobilek

Continuous Arterio-Venous Hemofiltration for the Treatment of Acute Renal Failure in Septic Shock / Wolfgang Reichow, Heinz Koehler, Klaus Dietrich, and Anton Schafmayer

The Continuous Arterio-Venous Hemofiltration in Shock / H.C. Rau, K.H. Staubach, C. Hohlbach, and W. Klingler

2.4. Corticosteroids

Corticosteroids in the Treatment of Septic Shock / William Schumer

Effect of Methylprednisolone, Prednisolone and Dexamethasone on Granulocyte Function and Complement Activation / Heinz Redl, Herbert Lamche, Eva Paul, Anna Schiesser, and Günther Schlag

Comparison of Different Corticosteroids in Rat Endotoxemia / Soheyl Bahrami, Anna Schiesser, Heinz Redl, and Günther Schlag

Can Preoperative High Dose Corticosteroids Preserve Normal Pulmonary Permeability and Homeostasis? / Lennart Smith, Svenerik Andreasson, Tom Saldeen, and Bo Risberg

2.5 Specific Measures

Influence of Parenteral Nutrition on Lung Surfactant in the Traumatized Rat / Soheyl Bahrami, Harald Gasser, Wolfgang Strohmaier, Heinz Redl, and Günther Schlag

Effects of Surfactant Replacement on Respiratory Failure Induced by Free Oxygen Radicals / B. Lachmann, O.D. Saugstad, and W. Erdmann

Glucose-Insulin-Potassium (GIK) in Hypodynamic Septic Shock / Walter Mauritz, Ingrid Schindler, Ernst Zadrobilek, and Paul Sporn

Non-Adrenergic Inotropic Support in Septic Shock / Marc Domb, Corinne De Boelpeape, and Jean-Louis Vincent

Effects of Endotoxin and Gadolinium Chloride on Acute Septic Peritonitis and Septic Shock in Rats / George Lázár, Jr., Elizabeth Husztik, and George Lázár

Contributors

Ansgar O. Aasen, Surgical Department, Ullevaal Hospital, University of Oslo, 0407 Oslo 4, Norway [133,185,193,211,227]

Svenerik Andreasson, Department of Anesthesiology, East Hospital, Göteborg, Sweden [133]

P. Angiolini, Institute of Anesthesiology and Intensive Therapy, University Policlinico di Careggi, 50134 Florence, Italy [259]

Frederick Aono, Department of Life Sciences, Travenol Laboratories, Inc., Round Lake, IL 60073 [333]

Soheyl Bahrami, Ludwig Boltzmann Institute for Experimental Traumatology, Vienna, Austria [347]

István Balogh, Institute of Forensic Medicine, Semmelweis Medical University, Budapest, Hungary 1082 [621]

William Bär, Material Chemical Works, Budapest, Hungary 1734 [633]

Robert E. Barrow, Department of Research, Shriners Burns Institute, Galveston, TX 77550 [539]

Elizabeth Basalka, Sandoz Forschungsinstitut, A-1235 Vienna, Austria [427]

G. I. J. M. Beerthuisen, Department of General Surgery, University Hospital St. Radboud, Nijmegen, The Netherlands [495]

Kristina E-dr. Behm, Clinical Research Center, University Hospital, Linköping, Sweden [63]

H. J. M. Beijer, Experimental Laboratory for Peripheral Circulation, University Hospital Utrecht, Utrecht, The Netherlands [495]

Anders Bengtson, Department of Anesthesiology, Sahlgren's Hospital, Göteborg, Sweden [3,11]

Maj-Britt Bengtsson, Clinical Research Center, University Hospital, Linköping, Sweden [63]

M. Biasiucci, Intensive Care Department, II Faculty of Medicine, University of Naples, Napoli, Italy [271]

Peter Bie, Department of Medical Physiology, Panum Institute and Hvidovre Hospital, University of Copenhagen, Copenhagen, Denmark [629]

Serge Blécic, Department of Intensive Care, Erasme University Hospital, Free University of Brussels, Brussels, Belgium [393]

The numbers in brackets are the opening page numbers of the contributors' articles.

Günther Blümel, Department of Experimental Surgery, Technical University, 8000 Munich 80, Federal Republic of Germany [419]

Roger C. Bone, Rush-Presbyterian-St. Luke's Medical Center, Chicago, Illinois 60612 [327]

Julian Borgia, Department of Life Sciences, Travenol Laboratories, Inc., Round Lake, IL 60073 [333]

Edmund C. Burke, Department of Physiology, Louisiana State University Medical Center, New Orleans, LA 70112 [573]

Claude Celotto, Institute of Biochemistry, University of Graz, A-8010 Graz, Austria [245]

G. A. Charbon, Experimental Laboratory for Peripheral Circulation, University Hospital Utrecht, Utrecht, The Netherlands [495]

M. Cianciulli, Intensive Care Department, II Faculty of Medicine, University of Naples, Napoli, Italy [271]

C. Clasen, Krankenhaus Itzehoe, 2210 Itzehoe, Federal Republic of Germany [175]

C. G. Cochrane, Research Institute of Scripps Clinic, San Diego, CA 92103 [253]

Farag I. Coraim, Department of Anaesthesiology and Intensive Care Medicine, The University of Vienna, Vienna A-1090, Austria [611]

R. Cuocolo, Intensive Care Department, II Faculty of Medicine, University of Naples, Napoli, Italy [271]

Ion V. Deaciuc, Department of Physiology, Louisiana State University Medical Center, New Orleans, LA 70112 [401]

Corinne De Boelpaepe, Department of Intensive Care, Erasme University Hospital, Free University of Brussels, Brussels, Belgium [393]

Robert H. Demling, Longwood Area Trauma Center, Harvard Medical School, Boston, MA 02115 [525]

Claudio Denzlinger, Biochemisches Institut, University of Freiburg, D-7800 Freiburg, Federal Republic of Germany [301]

László Dézsi, Experimental Research Department, Semmelweis University Medical School, Budapest, Hungary [503]

Hans P. Dinges, Institute of Pathology, University of Graz, Graz, Austria [43]

Heinrich Ditter, Department of Internal Medicine, Justus-Liebig University, D-6300 Giessen, Federal Republic of Germany [369]

Marc Domb, Department of Intensive Care, Erasme University Hospital, Free University of Brussels, Brussels, Belgium [393]

Hermann Esterbauer, Institute of Biochemistry, University of Graz, A-8010 Graz, Austria [245]

Erzsébet Fehér, Department of Anatomy, Semmelweis University Medical School, Budapest, Hungary [503]

E. Fink, Abteilung für Klinische Chemie und Klinische Biochemie, Chirurgische Klinik Innenstadt der Universität München, D-8000 München 2, Federal Republic of Germany [159]

Keith N. Frayn, MRC Trauma Unit, University of Manchester, Manchester M13 9PT, United Kingdom [463]

H. Fritz, Abteilung für Klinische Chemie und Klinische Biochemie, Chirurgische Klinik Innenstadt der Universität München, D-8000 München 2, Federal Republic of Germany [127]

Günther Fuhrer, Department of Thoracic and Cardiovascular Surgery, University of Tübingen, D-7400 Tübingen, Federal Republic of Germany [87, 107]

Michael J. Gallimore, Department of Thoracic and Cardiovascular Surgery, University of Tübingen, D-7400 Tübingen, Federal Republic of Germany [87]

R. Geiger, Abteilung für Klinische Chemie und Klinische Biochemie, Chirurgischen Klinik der Universität München, D-8000 München 2, Federal Republic of Germany [115]

Alfred Geißler, Institute for Experimental Medicine, University of Cologne, D-5000 Cologne, Federal Republic of Germany [95]

Anna Gergely, National Institute of Nutrition, Budapest, Hungary 1097 [621]

Anders Gidlöf, Clinical Research Center, University Hospital, Linköping, Sweden [63]

E. Gono, Abteilung Arbeitsmedizin, Medizinische Einrichtungen der Universität-Gesamthochschule Essen, Essen, Federal Republic of Germany [517]

R. Jan. A. Goris, Department of General Surgery, University Hospital St. Radboud, Nijmegen, The Netherlands [55, 495]

A. B. Johan Groeneveld, Department of Internal Medicine, Medical Intensive Care Unit, Free University Hospital, Amsterdam, The Netherlands [487]

Wolfgang Hagmann, Biochemisches Institut, University of Freiburg, D-7800 Freiburg, Federal Republic of Germany [301]

Seth Hallström, Ludwig Boltzmann Institute for Experimental Traumatology, Vienna, Austria [591]

János Hamar, National Institute of Traumatology, Semmelweis University Medical School, Budapest, Hungary [503]

Dale E. Hammerschmidt, Hematology Division, Department of Medicine, University of Minnesota, Minneapolis, MN 55455 [19]

Peter Heckenast, Institute of Biochemistry, University of Graz, A-8010 Graz, Austria [245]

Mats Heideman, Department of Surgery I, Sahlgren's Hospital, Göteborg, Sweden [3,11]

Wolfgang Heller, Department of Thoracic and Cardiovascular Surgery, University of Tübingen, D-7400 Tübingen, Federal Republic of Germany [87, 107]

David N. Herndon, Department of Surgery, Shriners Burns Institute, Galveston, TX 77550 [539]

James G. Hilton, Department of Pharmacology, Shriners Burns Institute, Galveston, TX 77550 [539]

D. B. Hinshaw, Research Institute of Scripps Clinic, San Diego, CA 92103 [253]

Susanne Hoberg, Department of Thoracic and Cardiovascular Surgery, University of Tübingen, D-7400 Tübingen, Federal Republic of Germany [107]

H. Hoffmann, Abteilung für Klinische Chemie und Klinische Biochemie, Chirurgische Klinik Innenstadt der Universität München, D-8000 München 2, Federal Republic of Germany [115,127,159]

Hans-Eberhard Hoffmeister, Department of Thoracic and Cardiovascular Surgery, University of Tübingen, D-7400 Tübingen, Federal Republic of Germany [87,107]

Pia Holmberg, Department of Anesthesiology, Sahlgren's Hospital, Göteborg, Sweden [11]

Geza Horpacsy, Institute for Experimental Medicine, University of Cologne, D-5000 Cologne, Federal Republic of Germany [95]

Werner Hügel, Institute for Experimental Medicine, University of Cologne, D-5000 Cologne, Federal Republic of Germany [95]

P. A. Hyslop, Research Institute of Scripps Clinic, San Diego, CA 92103 [253]

Wilfried Ilias, Second Surgical Department, The University of Vienna, Vienna, Austria [611]

Elizabeth Rogers Jacobs, University of Arkansas for Medical Sciences, Little Rock, AR 72205; present address: Rush-Presbyterian-St. Luke's Medical Center, Chicago, IL 60612 [327]

Gary J. Jesmok, Department of Life Sciences, Travenol Laboratories, Inc., Round Lake, IL 60073 [333]

Marianne Jochum, Abteilung für Klinische Chemie und Biochemie, Chirurgischen Klinik Innenstadt der Universität München, D-8000 München 2, Federal Republic of Germany [121,175,509]

Theo Joka, Abteilung Unfallchirurgie, Medizinische Einrichtungen der Universität-Gesamthochschule Essen, Essen, Federal Republic of Germany [311,509,517]

Miklós Juhász, O. Korvin Hospital, 1071 Budapest, Hungary [503]

Dietrich Keppler, Biochemisches Institut, University of Freiburg, D-7800 Freiburg, Federal Republic of Germany [301]

J. Knöllner, Institut für Medizinische, Mikrobiologie und Immunologie, Bochum, Federal Republic of Germany [311]

Ernst Koller, Institute of Biochemistry, University of Graz, A-8010 Graz, Austria [245]

W. König, Institut für Medizinische, Mikrobiologie und Immunologie, Bochum, Federal Republic of Germany [311,317]

K.-H. Konz, Medizinische Klinik, Abteilung Kardiologie, University of Tübingen, Tübingen, Federal Republic of Germany [281]

Ernst Kreuzfelder, Medizinische Virologie und Immunologie, Universitätsklinikum Essen, Essen, Federal Republic of Germany [509]

Peter Krösl, Ludwig Boltzmann Institute for Experimental Traumatology, Vienna, Austria [561,591]

Karel Kubat, Department of Pathology, University Hospital St. Radboud, Nijmegen, The Netherlands [55]

Charles Lam, Sandoz Forschungsinstitut, A-1235 Vienna, Austria [427]

Dagmar Langner, Department of Experimental Surgery, Technical University, 8000 Munich 80, Federal Republic of Germany [419]

Günther Laufer, Second Surgical Department, The University of Vienna, Vienna A-1090, Austria [611]

David H. Lewis, Clinical Research Center, University Hospital, Linköping, Sweden [63]

Rod A. Little, MRC Trauma Unit, University of Manchester, Manchester M13 9PT, United Kingdom [463]

Joachim Lutz, Department of Physiology, University of Würzburg, Würzburg, Federal Republic of Germany [503]

Pascal Luybaert, Department of Intensive Care, Erasme University Hospital, Free University of Brussels, Brussels, Belgium [393]

Asrar B. Malik, Department of Physiology, Albany Medical College of Union University, Albany, NY 12208 [33]

G. Martini, Institute of Anesthesiology and Intensive Therapy, University Policlinico di Careggi, 50134 Florence, Italy [259]

F. Reinhard Matthias, Department of Internal Medicine, Justus-Liebig University, D-6300 Giessen, Federal Republic of Germany [369]

Kathleen H. McDonough, Department of Physiology, Louisiana State University Medical Center, New Orleans, LA 70112 [573]

Jesper Mehlsen, Department of Medical Physiology, Panum Institute and Hvidovre Hospital, University of Copenhagen, Copenhagen, Denmark [629]

Angela Menschik, Cardiovascular Research Laboratories, AB Hässle, Mölndal, Sweden [63]

Fred Mihm, Ludwig Boltzmann Institute for Experimental Traumatology, Vienna, Austria [347]

K. M. Moser, University of California Medical Center, San Diego, CA 92103 [203]

Robert Moser, Institute of Biochemistry, University of Graz, A-8010 Graz, Austria [245]

W. Mueller-Esterl, Abteilung für Klinische Chemie und Klinische Biochemie, Chirurgische Klinik Innenstadt, Universität München, 8000 München 2, Federal Republic of Germany [175]

Hugo Müller, Institute for Experimental Medicine, University of Cologne, D-5000 Cologne, Federal Republic of Germany [95]

Froye Naess, Surgical Department, Ullevaal Hospital, University of Oslo, Oslo, Norway [185]

Sandor Nagy, Institute of Experimental Surgery, University Medical School of Szeged, Szeged, Hungary [599]

Heinz Neuhof, Department of Internal Medicine, Division of Clinical Pathophysiology and Experimental Medicine, Justus Liebig University, 6300 Giessen, Federal Republic of Germany [289]

G. P. Novelli, Institute of Anesthesiology and Intensive Therapy, University Policlinico di Careggi, 50134 Florence, Italy [259]

Hans K.S. Nuytinck, Department of General Surgery, University Hospital St. Radboud, Nijmegen, The Netherlands [55]

Susanne Oberste-Beulmann, Unfallchirurgie, Universitätsklinikum Essen, Essen, Federal Republic of Germany [509]

Udo Obertacke, Abteilung Unfallchirurgie, Medizinische Einrichtungen der Universität-Gesamthochschule Essen, Essen, Federal Republic of Germany [509,517]

Xavier J.M.W. Offermans, Department of General Surgery, University Hospital St. Radboud, Nijmegen, The Netherlands [55]

O. Ortolani, Intensive Care Department, II Faculty of Medicine, University of Naples, Napoli, Italy [271]

Eva Paul, Ludwig Boltzmann Institute for Experimental Traumatology, Vienna, Austria [165]

Anton Philapitsch, Immuno Hämoderivate AG, A-1220 Wien, Austria and Department of Thoracic and Cardiovascular Surgery, University of Tübingen, D-7400 Tübingen, Federal Republic of Germany [107,141,159]

Johan Pillgram-Larsen, Surgical Department, Ullevaal Hospital, University of Oslo, 0407 Oslo 4, Norway [185,193,211,227]

Ulrich Pison, Abteilung Unfallchirurgie, Medizinische Einrichtungen der Universität-Gesamthochschule Essen, Essen, Federal Republic of Germany [317,509,517]

Susan Pollak, Material Chemical Works, Budapest, Hungary 1743 [633]

Heinz Redl, Ludwig Boltzmann Institute for Experimental Traumatology, Vienna, Austria [xxv,43,165,347,591]

Hubert Reichle, Department of Anaesthesiology, University of Munich, 8000 Munich 70, Federal Republic of Germany [419]

Bo Risberg, Department of Surgery I, Sahlgrenska Hospital, Göteborg, Sweden [133]

Bryan L. Roth, Naval Medical Research Institute, Bethesda, MD 20814 [401]

Elizabeth Röth, Department of Experimental Surgery, University of Medicine, Pécs, Hungary 7643 [633]

Peter Röttger, Department of Pathology, General Hospital, D-5160 Düren, Federal Republic of Germany [369]

Tom E. Ruud, Surgical Department, Ullevaal Hospital, University of Oslo, 0407 Oslo 4, Norway [185,193,211,227]

Kåre Sander-Jensen, Department of Medical Physiology, Panum Institute and Hvidovre Hospital, University of Copenhagen, Copenhagen, Denmark [629]

Anna Schiesser, Ludwig Boltzmann Institute for Experimental Traumatology, Vienna, Austria [165,347]

Günther Schlag, Ludwig Boltzmann Institute for Experimental Traumatology, Vienna, Austria [xxv,43,165,347,561,591]

K. P. Schmit-Neurburg, Abteilung Unfallchirurgie, Medizinische K.P. Schmit-Neurburg, Abteilung Einrichtungen der Universität-Gesamthochschule, Essen, Federal Republic of Germany [317]

Wolfgang Schönfeld, Institut Für Medizinische Mikrobiologie und Immunologie, Universität Bochum, Bochum, Federal Republic of Germany [311,509]

I. U. Schraufstatter, Research Institute of Scripps Clinic, San Diego, CA 92103 [253]

Hans-Peter Schuster, Medizinische Klinik I, Städtisches Krankenhaus Hildesheim, D-3200 Hildesheim, Federal Republic of Germany [459]

Eberhard Schütze, Sandoz Forschungsinstitut, A-1235 Vienna, Austria [427]

Werner Seeger, Department of Internal Medicine, Division of Clinical Pathophysiology and Experimental Medicine, Justus Liebig University, 6300 Giessen, Federal Republic of Germany [289]

P. Sefrin, Institute of Anaesthesiology, University of Würzburg, D-8700 Würzburg, Federal Republic of Germany [477]

William C. Shoemaker, Department of Surgery, Los Angeles County King-Drew Medical Center, University of California, Los Angeles, Los Angeles, CA 90059 [361]

M. Siebeck, Chirurgische Klinik Innenstadt, Universität München, D-8000 München 2, Federal Republic of Germany [115,121,127,141,159]

John H. Siegel, Department of Surgery Johns Hopkins University and Department of Surgery, Maryland Institute for Emergency Medical Services Systems, University of Maryland, Baltimore, MD 21201 [439]

Janet Simpson, Department of Life Sciences, Travenol Laboratories, Inc., Round Lake, IL 60073 [333]

Lani W. Smith, Department of Physiology, Louisiana State University Medical Center, New Orleans, LA 70112 [573]

Lennart Smith, Department of Surgery I, Sahlgrenska Hospital, Göteborg, Sweden [133]

R. M. Smith, University of California Medical Center, San Diego, CA 92103 [203]

John J. Spitzer, Department of Physiology, Louisiana State University Medical Center, New Orleans, LA 70112 [573]

Judy A. Spitzer, Department of Physiology, Louisiana State University Medical Center, New Orleans, LA 70112 [401]

R. G. Spragg, University of California Medical Center, San Diego, CA 92103 [203,253]

Jan. O. Stadaas, Surgical Department, Ullevaal Hospital, University of Oslo, 0407 Oslo 4, Norway [185,193,211,227]

Carsten Stadeager, Department of Medical Physiology, Panum Institute and Hvidovre Hospital, University of Copenhagen, Copenhagen, Denmark [629]

J. Sturm, Medizinische Hochschule Hannover, Hannover, Federal Republic of Germany [311]

Norbert Suttorp, Department of Internal Medicine, Division of Clinical Pathophysiology and Experimental Medicine, Justus-Liebig University, 6300 Giessen, Federal Republic of Germany [289]

Kornél Szabó, Burn Center, Central Hospital, Budapest, Hungary 1553 [621]

R. Tani, Institute of Anesthesiology and Intensive Therapy, University Policlinico di Careggi, 50134 Florence, Italy [259]

O. Thetter, Chirurgische Klinik Innenstadt, Universität München, D-8000 München 2, Federal Republic of Germany [121,127,159]

Lambertus G. Thijs, Department of Internal Medicine, Medical Intensive Care Unit, Free University Hospital, Amsterdam, The Netherlands [487]

Martin Thurnher, Ludwig Boltzmann Institute for Experimental Traumatology, Vienna, Austria [347]

G. Tiegs, Physiologisch-Chemisches Institut, University of Tübingen, Tübingen, Federal Republic of Germany [281]

Gerd O. Till, Department of Pathology, University of Michigan Medical School, Ann Arbor, MI 48109 [235]

Bela Török, Department of Experimental Surgery, University of Medicine, Pécs, Hungary 7643 [633]

Daniel L. Traber, Department of Anesthesiology and Physiology, University of Texas Medical Branch; and Department of Anesthesia Research, Shriners Burn Institute, Galveston, TX 77550 [149,377,539]

A. Trebbi, Intensive Care Department, II Faculty of Medicine, University of Naples, Napoli, Italy [271]

Elena R. Turco, Department of Physiology, Louisiana State University Medical Center, New Orleans, LA 70112 [401]

Philippe Van der Linden, Department of Intensive Care, Erasme University Hospital, Free University of Brussels, Brussels, Belgium [393]

Gregory M. Vercellotti, Hematology Division, Department of Medicine, University of Minnesota, Minneapolis, MN 55455 [19]

Jean-Louis Vincent, Department of Intensive Care, Erasme University Hospital, Free University of Brussels, Brussels, Belgium [393]

Christa Vogl, Ludwig Boltzmann Institute for Experimental Traumatology, Vienna, Austria [347,591]

Reinhard Voss, Department of Internal Medicine, Justus-Liebig University, D-6300 Giessen, Federal Republic of Germany [369]

Hubert Walzl, Sandoz Forschungsinstitut, A-1235 Vienna, Austria [427]

Jørgen Warberg, Department of Medical Physiology, Panum Institute and Hvidovre Hospital, University of Copenhagen, Copenhagen, Denmark [629]

Peter A. Ward, Department of Pathology, University of Michigan Medical School, Ann Arbor, MI 48109 [235]

H. F. Welter, Chirurgische Klinik Innenstadt, Universität München, D-8000 München 2, Federal Republic of Germany [121,127,141]

A. Wendel, Physiologisch-Chemisches Institut, University of Tübingen, Tübingen, Federal Republic of Germany [281]

Peter Wendt, Department of Experimental Surgery, Technical University, 8000 Munich 80, Federal Republic of Germany [419]

Stephen Westaby, Royal Postgraduate Medical School, Hammersmith Hospital, London, UK [75]

H. Wiesinger, Pathologisches Institut,
Universität München, D-8000 München
2, Federal Republic of Germany [141]

Claudia Wilfing, Ludwig Boltzmann
Institute for Experimental
Traumatology, Vienna, Austria [165]

Frank J. Wilson, Jr., University of
Oklahoma Health Sciences Center,
Oklahoma City, OK 73104 [327]

Gregor Wollenek, Second Surgical
Department, The University of Vienna,
Vienna A-1090, Austria [611]

Ernst Wolner, Second Surgical
Department, The University of Vienna,
Vienna A-1090, Austria [611]

Gerda Zilow, Department of
Immunologie, Universität Heidelberg,
Heidelberg, Federal Republic of
Germany [509]

FEASIBILITY STUDY OF VERY HIGH APROTININ DOSAGE IN
POLYTRAUMA PATIENTS

C. Clasen*, M. Jochum**, and W. Mueller-Esterl**

* Anästhesiol. Intensivabteilung, Krankenhaus
Itzehoe, 2210 Itzehoe, F.R.G.

** Abt. f. Klin.Chemie u. Klin. Biochemie,
Chirurg. Klinik Innenstadt

d. Universität München, 8000 München 2, F.R.G.

INTRODUCTION

Polytrauma patients at risk to develop adult respiratory distress syndrome (ARDS) and/or multiple organ failure present a great therapeutic challenge. Newly developed concepts on the role of proteolysis, proteases (e.g. plasma kallikrein, plasmin) and proteolytic breakdown products (e.g. fibrin degradation products) in the pathogenesis of these diseases stimulated us to reconsider the role of proteinase inhibitors as therapeutic agents in polytrauma and shock (Manwaring and Curreri, 1982; Schapira et al., 1983, 1985). The inhibitor that has most widely been used in this indication is the proteinase inhibitor from bovine lung, aprotinin or Trasylol^R (Verstraete, 1985; Fritz and Wunderer, 1983). Aprotinin inhibits proteinases such as kallikrein, plasmin and trypsin with high affinity. Theoretical considerations based on enzyme kinetics and substrate availability suggested that an aprotinin concentration of about 200 KIU (kallikrein inactivator units) per ml plasma (corresponding to 4 $\mu\text{mol/l}$) would suffice to effectively control and inhibit plasma kallikrein as well as systemic fibrinolysis executed by plasmin (Philipp, 1978; Fritz and Wunderer, 1983). Only recently it has become possible to relate empirical dosage with actual aprotinin plasma levels in patients. Specific, fast and reliable test procedures have been established, i.e. an enzymatic kallikrein inhibition test (Jochum et al., 1984) and an enzyme-linked immunosorbent assay specific for aprotinin (Mueller-Esterl et al., 1984).

The question was then, whether it would be possible in a clinical situation to obtain plasma concentrations of the exogenous inhibitor which are high enough to provide the predicted inhibition of plasma kallikrein. Here we report on a clinical feasibility study in polytrauma patients with the aim of obtaining more data about aprotinin plasma levels and especially of examining the tolerability of aprotinin given in elevated dosage. In the first part of this study a moderately increased aprotinin dose per patient was applied, in the second part the dosage was very high as compared to previously reported clinical work.

PATIENTS AND METHODS

The following admission criteria were observed: Patients selected for the study had been brought to the accident department immediately after having suffered severe injury with polytrauma, defined as external blood loss greater than 500 ml, multiple bone fractures, extensive soft tissue trauma and involvement of intra-thoracic or intra-abdominal lesions. Excluded were patients with severe head injuries requiring neurosurgery and patients where first medical aid had been delayed (more than 30 minutes after the accident) or where the start of the aprotinin infusion was not possible within the first hour after the time of accident.

Preclinical therapy consisted of immediate intubation followed by ventilation with PEEP, initial volume replacement in the ambulance with colloids (gelatine) and electrolytes, sedation (flunitrazepam), and analgetic support (fentanyl). Clinical management included continuous ventilation, further infusion of crystalloid solutions until circulatory stabilization and adequate excretion was reached, continued analgesia and sedation, dopamine 4 $\mu\text{g}/\text{kg}/\text{min}$, nitroglycerine 2 mg/h, heparin for thrombosis prophylaxis and ranitidine together with antacids for the prophylaxis of stress ulcers. Surgical management followed the principles of Wolff et al. (1978) which are aimed at the prevention of post-traumatic complications by an optimal coordination of surgery and intensive care.

Patients fulfilling the admission criteria were given additional infusions of aprotinin. Two dosage regimens were applied: Group I received a total dose of 6 million KIU (kallikrein inactivator units) by discontinuous application

within 36 hours (2 million KIU initially over 30 min; 1 million KIU at 6, 12, and 18 hours; 0.5 million KIU at 24 and 36 hours). Group II received within 24 hours a total dose of 17.5 million KIU (2.5 million KIU initially; continuous i.v. infusion of 1 million KIU/h for 12 hours, followed by 0.25 million KIU/h for another 12 hours). Aprotinin was supplied as Trasylol^R infusion 500,000 KIU in 50 ml flasks from Bayer AG, Leverkusen (Germany).

Blood samples were taken before the infusion was started and 0.5, 1, 2, 4, 6, 9, 12, 15, 18, 24, 36, and 48 hours later. Out of these plasma was prepared and deep frozen immediately. Plasma concentrations of aprotinin were determined by ELISA according to the method described by Mueller-Esterl (1984). Plasmin inhibiting capacity in plasma was determined by chromogenic substrate assay with S-2251 (Deutsche KabiVitrum GmbH, München). For the immunological assay of α_2 -antiplasmin rocket immuno-electrophoresis according to Laurell (1972) using specific antibodies (Behring Werke AG, Marburg) was applied.

Data were biometrically evaluated in a descriptive manner. Aprotinin plasma levels are given as median values with ranges between the 25 % and 75 % quartils. Graphs represent mean values and standard deviation, if not otherwise indicated.

RESULTS

At total of 23 severely injured patients were admitted according to the criteria described above. Table 1 summarizes the main characteristics of the patients investigated.

Sex Distribution	13 male, 10 female
Mean Age	men: 29.5 years women: 43.6 years
Mortality	n = 4 (17 %)
Sepsis	n = 10 (42 %)
Respiratory Failure (ARDS)	n = 5 (21 %)
Artificial Respiration	\bar{x} = 9.7 days
Stay in ICU	\bar{x} = 13.9 days
Transfusion Requirement	\bar{x} = 15.5 units of blood

Table 1. Main characteristics and outcome of 23 poly-trauma patients.

In the first series of 10 patients receiving intermittent bolus application of aprotinin, plasma samples were taken at 6, 12, 18, 24, and 36 hours just before the next infusion was started. Therefore, the aprotinin levels obtained from group I represent trough values. The discontinuous dosage schedule of group I (6 million KIU aprotinin within 36 hours) resulted in transitory plasma levels of aprotinin ranging from 100 to 200 KIU/ml (2 - 4 $\mu\text{mol/l}$), which then declined within 6 hours to 15 - 20 KIU/ml (about 0.3 $\mu\text{mol/l}$). This trough value concentration of aprotinin could be maintained by repeated re-infusions of 1 million KIU every 6 hours. 12 hours after the last infusion plasma levels were below 5 KIU/ml (0.1 $\mu\text{mol/l}$) (Fig. 1).

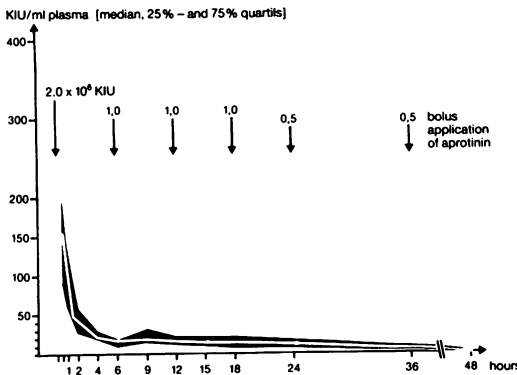


Figure 1. Aprotinin concentration in patient plasma (Group I, n = 10)

The continuous dosage schedule of group II (17.5 million KIU aprotinin within 24 hours) resulted in initial peak plasma levels of about 400 KIU/ml (8 $\mu\text{mol/l}$) which returned to 100 - 150 KIU/ml during subsequent continuous infusion of 1 million KIU/h over 12 hours. Under the infusion of the reduced dose of 0.25 million KIU/h the plasma level fell further to about 50 KIU/ml plasma. 24 hours after the aprotinin infusion was finished, plasma levels were below 15 KIU/ml (0.3 $\mu\text{mol/l}$) in all cases, with a median value of only 2.5 KIU/ml (Fig. 2).

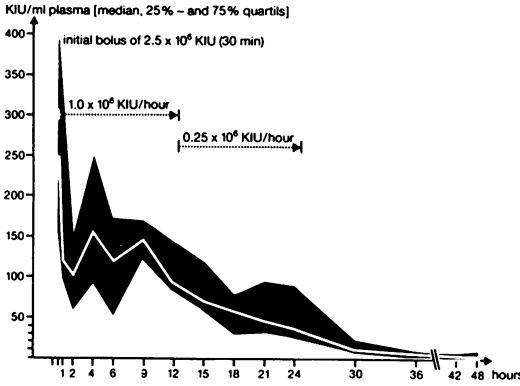


Figure 2. Aprotinin concentration in patient plasma (Group II, n = 13)

Plasmin inhibiting capacity was measured in plasma samples of patients from both dosage groups. Fig. 3a and 3b are representative examples of one patient each, demonstrating sufficient correlation between aprotinin antigen levels and antiplasmin activity assayed enzymatically. The natural

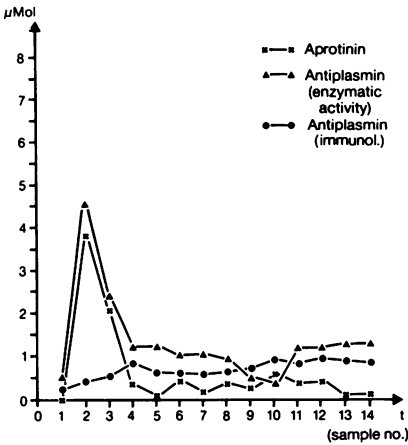


Figure 3a. (Group I)

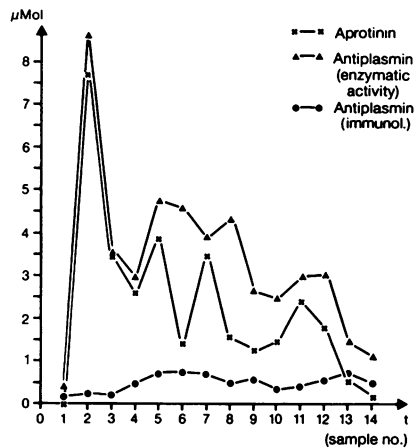


Figure 3b. (Group II)

Plasmin inhibiting capacity in plasma from 1 patient

plasmin inhibitor in plasma, α_2 -antiplasmin, as determined immunologically was rather low in the beginning ($<1 \mu\text{mol/l}$) and there was only a slight increase during the early phase of treatment. Among the routine coagulation tests no major changes during the period of high aprotinin plasma levels have been observed (data not shown). As an example Fig. 4 demonstrates prothrombin time for both dosage groups at 6 hours and 24 hours after start of treatment without any particular differences.

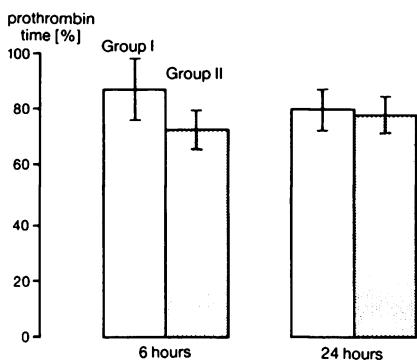


Figure 4. Prothrombin time at 6 and 24 hours

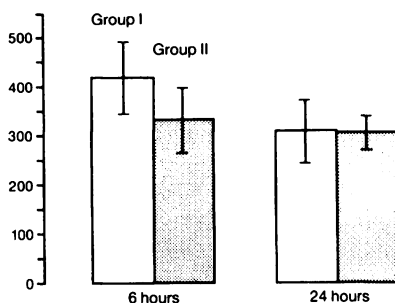


Figure 5. p_{aO_2}/FIO_2 ratio at 6 and 24 hours

Lung function was assessed by monitoring the p_{aO_2}/FIO_2 ratio (Fig. 5). Although group II with the higher aprotinin dosage tended to exhibit a more stable situation as compared to group I, there were no obvious differences in this parameter between both groups after 24 hours.

Urine output was measured continuously and volumes were calculated in ml/h. Fig. 6 shows the course of average urine production per hour over the initial 48 h-period for both dosage groups. There was an increase of urine output from 288 ml/h to 392 ml/h in the high dosage group II during the second half of the first 12 h-period when 1 million KIU aprotinin per hour was given by continuous infusion. This increase in urine output was suspended following the reduction of aprotinin dosage after 12 hours (from 1 million KIU to 0.25 million KIU/h), but the average ml/h in group II remained higher than in group I.

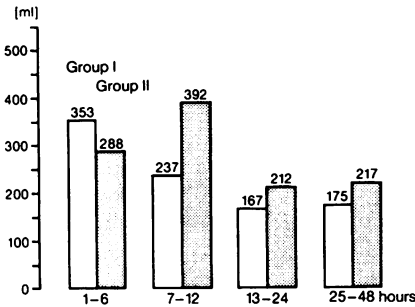


Figure 6.
Average urine output per hour (mean values)

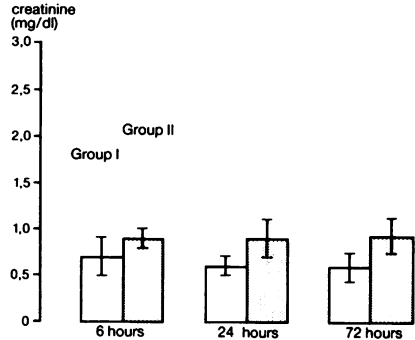


Figure 7.
Serum creatinine at 6, 24, and 72 hours after start of aprotinin

Serum creatinine concentrations had been determined at 6, 24, and 72 hours after start of treatment. They remained in the normal range throughout the observation period, with no apparent differences between both dosage groups (Fig. 7).

DISCUSSION

Plasma levels of aprotinin as determined in this study followed in general the predicted course calculated from the pharmacokinetic constants of this inhibitor (Kaller et al., 1978). To secure a continuously elevated plasmatic concentration the dosage scheme with intermittent administration is clearly not suitable (group I). By contrast, the alternative application scheme applying continuous infusion (group II) ensured aprotinin plasma concentration within the desired range of 100 - 200 KIU/ml over a period of 12 hours. However, a considerable interindividual variation from patient to patient was observed, probably because patient-related differences in metabolism and excretion could not be excluded; yet this needs further investigation. Our results are in line with those of Dittmer (1985), who found also in polytrauma patients aprotinin plasma levels between 40 and 50 KIU/ml during continuous infusion of 250,000 KIU/h.

Tolerability of very high doses of aprotinin was apparently good. Neither coagulatory nor microcirculatory disturbances due to the trial drug have been observed. The incidence of pulmonary complications in our study was comparable to that reported for polytrauma in the recent literature (Johnson et al., 1985). Special attention was given to renal function during high aprotinin dosage. Whether the observed temporary increase in urine output in Group II was an effect of aprotinin or a chance finding cannot be decided at the moment. In fact, there have been similar observations made recently with high continuous administration of aprotinin (F. Schumann, personal communication). Impairment of renal function due to aprotinin application has not been observed in our patients.

In summary, our study has shown that a dosage schedule of aprotinin resulting - at least temporarily - in plasma levels of 200 KIU/ml is clinically feasible. It must be emphasized, however, that due to the design of this study and the limited number of patients investigated as yet no conclusion concerning effectiveness is allowed.

REFERENCES

- Fritz H, Wunderer G (1983). Biochemistry and applications of aprotinin, the kallikrein inhibitor from bovine organs. *Arzneim-Forsch/Drug Res* 33: 479-494.
- Dittmer H (1985). "Der polytraumatisierte Patient - Eine Analyse klinischer und pathobiochemischer Parameter" München: Med. Fakultät der Ludwig-Maximilians-Universität (Thesis).
- Jochum M, Jonáková V, Harke H, Fritz H (1984). Aprotininbestimmungen im Plasma: Methodik und erste klinische Ergebnisse. In Beck EA (ed): "Thrombose- und Hämostaseforschung 1984", Stuttgart - New York: Schattauer, pp 393-395.
- Johnson KD, Cadambi A, Seibert GB (1985). Incidence of adult respiratory distress syndrome in patients with multiple musculoskeletal injuries: Effect of early operative stabilization of fractures. *J Trauma* 25: 375-384.
- Kaller H, Patzschke K, Wegner LA, Horster FA (1978). Pharmacokinetic observations following intravenous administration of radioactive labelled aprotinin in volunteers. *Eur J Drug Metab Pharmacokin* 3: 79-85.
- Laurell CB (1972). Electro-immunoassay. *Scand J Clin Lab Invest* 29 (suppl 124): 21-37.

- Manwaring D, Curreri PW (1982). Platelet and neutrophil sequestration after fragment D-induced respiratory distress. *Circ Shock* 9: 75-80.
- Müller-Esterl W, Oettl A, Truscheit E, Fritz H (1984). Monitoring of aprotinin plasma levels by an enzyme-linked immunosorbent assay (ELISA). *Fresenius Z Anal Chem* 317: 718.
- Philipp E (1978). Calculations and hypothetical considerations on the inhibition of plasmin and plasma kallikrein by Trasylol. In Davidson JF, Rowan RM, Samama MM, Desnoyers PC (eds): "Progress in Chemical Fibrinolysis and Thrombolysis" New York: Raven Press, pp 291-295.
- Schapira M, Scott CF, Boxer LA, Colman RW (1983). Activation of human polymorphonuclear leukocytes by purified human plasma kallikrein. In Fritz H, Back N, Dietze G, Haberland GL (eds): "Kinins - III, part B", New York: Plenum Press, pp 747-753.
- Schapira M, Gardaz JP, Py P, Lew PD, Perrin LH, Suter PM (1985). Prekallikrein activation in the adult respiratory distress syndrome. *Bull Eur Physiopathol Respir* 21: 237-241.
- Verstraete M (1985). Clinical application of inhibitors of fibrinolysis. *Drugs* 29: 236-261.
- Wolf G, Dittmann M, Rüedi T, Buchmann B, Allgöwer M (1978). Koordination von Chirurgie und Intensivmedizin zur Vermeidung der posttraumatischen respiratorischen Insuffizienz. *Unfallheilkunde* 81: 425-442.

Index

- A23187 calcium ionophore, 290, 314, 315
Acidosis, cardiodepressant, 600
ADP-iron, cytotoxic lipid peroxidation products, rat liver microsomes, 247-249
Adrenal gland, catecholamines, multiple trauma, and ARDS, 479
Adrenaline. *See* Epinephrine
 α_1 -Adrenergic receptors, transmembrane signaling perturbation, endotoxemia, rat hepatocyte, 406-407, 415
 β -Adrenergic stimulation, myocardial dysfunction in sepsis, 576-577
 isoproterenol, 577, 578
Albumin flux, microvascular permeability, septic shock, 490-491
Aldehydes, lipid peroxidation products, rat liver microsomes, 245-249; *see also* Malondialdehyde (MDA)
Alveolar cell reactions, posttraumatic lung failure and ARDS, 509-514
 AaDO₂, 510
 bronchoalveolar lavage, 509-513
 chemiluminescence of neutrophils, 510, 511
 complement, 510, 512
 elastase, 510-513
 cf. vascular proteins, 513
 extravascular lung water, 510-512
 leukotrienes, 510-512
 polytrauma score, 510
 see also Bronchoalveolar lavage
Alveolar cells, type II, 103
Alveolar hypoxia, arachidonic acid system activation, isolated lung, 294-295
 α -Amanitin, 302, 306, 307
Amylase, aprotinin and C1 esterase inhibitor infusion and pancreatic shock, pig, 195
Anaphylatoxins (C3a and C5a). *See under* Complement activation
Angiotensin II, 382, 402
 heart stimulation, 599-600, 603-607
Antihistamines, multitherapy regimen for endotoxemia, pigs, 212, 213, 222, 228
Antioxidant drugs in shock therapy, 271-279
 ascorbic acid, 276
 BHT, 276
 vs. granulocyte aggregation, 276-277
 iron role, 272
 lipid peroxidation, 274-275
 vs. malondialdehyde formation, 276, 278
 α -MPG, 276
 natural systems, 272
 loss in shock, 273-275
 propyl-gallate, 276
 α -tocopherol, 276
 see also Oxygen free radical scavengers, prophylaxis and treatment of experimental shock, rat
Antioxidant protection vs. free radical mediated myocardial injury, dogs, 633-639
 ECG, 635
 GSH, 635-639
 ischemia-reperfusion, 634-639
 lipid peroxidation, 633-635, 638-639
 MDA, 635-636
 MTDQ-DA, 633, 636, 639
 SOD, 635-639
Antiplasmin
 multitherapyregimen for endotoxemia, pigs, 216, 219
 α_2 -, very high dosage aprotinin in polytrauma, 177, 180
Antiproteases. *See* Protease inhibitors in endotoxemia; specific inhibitors
Antithrombin III, 40
 C1-esterase inhibitor
 early *E. coli* septicemia, pigs, 142, 144
 and elastase release, extracorporeal circulation, 108, 111

- eglin, elastase inhibitor, and lung edema, septic pigs, 122–124
- kallikrein-kinin system activation, lung, *E. coli* septic sheep, 134, 136–138
- multitherapy regimen for endotoxemia, pigs, 212, 213, 216, 217, 220, 221, 228
- α_1 -Antitrypsin, C1-esterase inhibitor, early *E. coli* septicemia, pigs, 144
- Aortic endothelium, oxidant injury, cultured cells, 254–255
- Aorto-coronary bypass. *See* Cardio-pulmonary bypass
- Apnoe, extracorporeal circulation, biochemical lung monitoring during CPB, 96, 98–100, 103–104
- Apple II, 568
- Aprotinin
and kallikrein
activation, and C1-esterase inhibitor, 159–163
activation during CPB, 87–89, 91, 93
infused, kinin-induced pathology in ARDS development, pig, 127–130
MDF release during CPB, 611–615, 617–618
multitherapy regimen for endotoxemia, pigs, 212, 218, 220, 228
- Aprotinin and C1-esterase inhibitor infusion and pancreatic shock, pig 193–200
amylase, 195
hemodynamics, improved, 193
arterial pressure, 193, 195
cardiac output, 194–195
kallikrein, 194, 196–200
inhibition, 193–197, 199
kinin, 199
kininogen, 199
prekallikrein, 194, 196, 199, 200
survival rate, 193
- Aprotinin, cellular effects, 165–171
granulocyte function, 165–168, 170–171
elastase release, 166–169
phagocytosis, 169, 171
platelets, 165, 170, 171
superoxide radical, 165, 166, 169
SOD, 166
- Aprotinin, very high dosage, polytrauma, 175–182
 α_2 -antiplasmin, rocket immunoelectrophoresis, 177, 180
feasibility study, 176
infusion, 176–178, 181
kallikrein inhibition, 175–181
lung function, 180, 182
plasma levels, 178–181
plasmin inhibition, 179
renal function, 180–182
creatinine, 181
urine output, 180–181
tolerance, 182
- Aptoglobin, 272
- Arachidonic acid, 170, 260, 302, 305–307
ibuprofen and ETX-stimulated inflammation, 334, 342, 344
lipid peroxidation products, cytotoxic, rat liver microsomes, 235, 247
see also Eicosanoids; Prostaglandin *entries*; Thromboxanes
- Arachidonic acid system activation, isolated rabbit lung, 289–298
alveolar hypoxia, 294–295
bacterial toxins, 295–296
complement, 292–293, 295
granulocytes, 292, 296–298
elastase, 296
oxygen radicals, 296
and hemodynamics, pulmonary, 289–298
PAP, 292–295
kallikrein-kinin system, 289, 291, 292
leukotrienes, 291, 293, 296
prostaglandins, 289, 291, 294–296
thromboxanes, 291, 293–297
- ARDS (adult respiratory distress syndrome) and complement in shock, 4, 6
development, kinin-induced pathology, kallikrein infusion, pig, 127–130
elastase and leukocyte counts, septic pig lung, 115, 118
granulocyte mediation of tissue injury, 23–24
pulmonary membranes, 75, 76, 78, 83–84
leukostasis, quantitative estimation, 50
limb ischemia, C3a and C5a as mediators of inflammation, 11

- microvascular permeability, septic shock, 487
- MOF, wound inflammatory mediators and, 534
- oxidant injury, cultured cells, 253
- physiologic-metabolic correlations, septic shock, 441, 446
- α_1 -proteinase inhibitor bioavailability, injected vs. aerosolized, 203–204
- whole body inflammation, trauma patient autopsy study, 55–60
- see also* Alveolar cell reactions, posttraumatic lung failure and ARDS; Catecholamines, multiple trauma, and ARDS; Leukotrienes and lipid mediators in ARDS pathogenesis; Phospholipid lung profile, ARDS in polytrauma patients; Prostaglandin E_1 administration in ARDS, septic and post-surgery patients
- Aryl sulfatase, 379
- Ascorbic acid, 276
- ATP, oxidant injury, cultured cells, 254
- Atrium, left, extracorporeal circulation, biochemical lung monitoring during CPB, 96–98, 101, 102, 104
- Atropine and heart rate in hypotensive central hypovolemia, 629–631
- Autopsy, leukostasis estimation, posttraumatic lung, 45–49
- diagnoses, 46–47
- see also under* Inflammation, whole body
- Bacterial toxins, arachidonic acid system activation, isolated lung, 295–296
- Bacteroides fragilis*, 447
- B cells, 5, 380
- BHT, 276
- Bilirubin, 11, 13–15, 17
- Bioavailability. *See* α_1 -Proteinase inhibitor bioavailability, injected vs. aerosolized
- Blood. *See* Coagulation; Oxygen and blood flow, regional differences, early sepsis; Oxygen free radicals, LPS generation, fresh human blood
- Blood pressure
- aprotinin and C1 esterase inhibitor infusion and pancreatic shock, pig, 193, 195
- plasma kallikrein-kinin system activation, 160–161
- eglin, elastase inhibitor, and lung edema, septic pigs, 123
- ETX shock (*E. coli*), dog model, 394, 395, 398
- multitherapy regimen for endotoxemia, hemodynamics, 229–230
- oxygen and blood flow, regional differences in early sepsis, 501
- trypsin-induced shock, hemodynamics and proteolysis, 189–191
- Body temperature
- BW755C in endotoxemia, 355, 357, 355, 357
- ibuprofen and ETX-stimulated inflammation, 340, 341
- Bradykinin, 93, 185, 190, 192, 289, 292
- ETX, cause of mediator release in sepsis, 380, 385, 387, 388
- kallikrein-kinin system activation, lung, *E. coli* septic sheep, 137–138
- multitherapy regimen for endotoxemia, pigs, 220–221
- Branched chain amino acids
- cardiovascular abnormalities, septic shock, 449, 451, 454–456
- leucine as heart depressant factor, 601
- Bronchoalveolar lavage
- alveolar cell reactions, posttraumatic lung failure and ARDS, 509–513
- elastase- α_1 -PI complex and leukocyte counts, septic pig lung, 116–117, 115
- leukotriene generation, polytrauma patients with ARDS, 312–314
- and phospholipid lung profile, ARDS, 518, 520
- α_1 -proteinase inhibitor bioavailability, injected vs. aerosolized, 203–205
- Bronchoscopy, 205
- Burns
- MOF, wound inflammatory mediators and, 525, 526, 528, 532
- infected cf. uninfected, 527
- nickel

- and heart depressant factors, 600
 - myocardial damage, 622
- Burn shock and resuscitation, 539–552
 - compliance, pulmonary, 550
 - dog, 541, 550
 - extravascular lung water, 548–550
 - fluid resuscitation, 543, 544, 552
 - hemodynamics, 540–543
 - human, 542, 543, 551
 - inhalation injury, 544–552
 - CO₂, 546, 547, 551
 - intubation, 551–552
 - surfactant, 550–551
 - ventilation, 551
 - lymph, 549–550
 - microvascular permeability, 539–541, 549
 - mortality, 544, 545
 - plasma volume, 540–542
 - PMNs, 539–540, 547–549
 - pulmonary dysfunction, 544, 546
 - edema, 548–550, 552
 - sheep, 548, 551
 - thromboxanes, 541, 548
 - verapamil, 542
- Butylated hydroxytoluene, 276
- BW755C (NSAID) effect on endotoxemia, 302, 347–358
 - body temperature, 355, 357
 - cf. corticosteroids, 356–357
 - hemodynamics, 356–357
 - leukocytes, 347–350, 352, 353, 357
 - lipooxygenase and cyclooxygenase inhibition, 302, 347, 358
 - lymph flow, 347, 349, 353–355, 357
 - microvascular permeability, 348, 354, 357
 - platelets, 348, 351
 - rats, 347–352, 357
 - mortality, 349, 350
 - sheep, 347–349, 353–357
 - MPAP, 353, 357
 - thromboxane, 347, 350, 352, 355–357
- Calcium
 - binding, inotropic plasma substances, LMW, prolonged shock, 596
 - channel blockers, burn shock and resuscitation, 542; *see also* Verapamil
 - homeostasis, altered, myocardial dysfunction in sepsis, 579, 581, 583, 584, 587
 - transmembrane signaling perturbation, endotoxemia, rat hepatocyte, 401–405, 409–410, 413–416
 - IP₃-stimulated release, 413–415
- Camera, gamma, microvascular permeability, septic shock, 487, 491
- Capillaries. *See* Microvascular permeability, endotoxemia/septic shock
- Carbohydrate oxidation, flow or catabolic phase, 465, 466
- Carbon monoxide, inhalation injury, burn shock and resuscitation, 546, 547, 551
- Cardiac output
 - aprotinin and C1 esterase inhibitor infusion and pancreatic shock, pig, 194–195
- ETX
 - cause of mediator release in sepsis, 377, 381, 382, 385, 387, 388
 - shock (*E. coli*), dog model, 393–394, 396–398
 - ibuprofen and ETX-stimulated inflammation, 338, 340
 - multitherapy regimen for endotoxemia, hemodynamics, 216–218, 229, 233
 - myocardial dysfunction in sepsis, 575, 579, 584
 - oxygen and blood flow, regional differences in early sepsis, 496, 498
 - PGE₁ administration in ARDS, 361
 - physiologic-metabolic correlations, septic shock, 440–442
 - trypsin-induced shock, hemodynamics and proteolysis, 189–191
 - see also* Heart entries
- Cardiopulmonary bypass. *See* Kallikrein-kinin system activation during aorto-coronary bypass (CPB); *under* Extracorporeal circulation; Granulocytes, mediation of pulmonary membrane damage; Myocardial depressant factor
- Cardiovascular abnormalities, metabolic basis, 446–453, 455–456; *see also* Hemodynamics
- Catabolic phase, metabolic changes in injury, 463, 465–469

- cf. starvation, 465–466
 - Catalase, oxygen free radicals and lung injury, 238, 240, 272, 274
 - Catecholamines
 - heart stimulation, 599–600, 603–607
 - injury cf. sepsis, 469, 470
 - see also* Epinephrine (adrenaline)
 - Catecholamines, multiple trauma, and ARDS, 477–481, 483–486
 - activation of
 - complement, 477, 478
 - kallikrein-kinin system, 477
 - activation of coagulation system, 477, 479–481
 - fibrin, 480–481
 - fibrinogen, 480–481
 - thrombin, 479, 480, 485–486
 - epinephrine, 478, 483–486
 - erythrocytes, 479
 - norepinephrine, 478, 483–486
 - pituitary and adrenal glands, 479
 - trauma scores, 478, 480, 484
- Cathepsin G, 124
 - Ceruloplasmin, 272
 - C1-esterase inhibitor, 191
 - and aprotinin, plasma kallikrein-kinin system activation, 159–163
 - and complement in shock, 4
 - and endotoxemia, 153
 - multitherapy regimen, pigs, 212, 213, 220, 221, 228
 - kallikrein system activation during CPB, 89, 92, 93
 - see also* Aprotinin and C1-esterase inhibitor infusion and pancreatic shock, pig
 - C1-esterase inhibitor and elastase release, extracorporeal circulation, 107–113
 - antithrombin III, 108, 111
 - complement system inhibitor, 107
 - elastase- α_1 -proteinase inhibitor complex, 107, 112, 113
 - β -factor XIIa, 108, 110
 - heparin, 108
 - kallikrein-kinin system inhibitor, 107–110, 113
 - prekallikrein, 107–109, 113
 - C1-esterase inhibitor, early *E. coli* septicemia, pigs, 141–146
 - antithrombin III, 142, 144
 - α_1 -antitrypsin, 144
 - factor XIII, 142, 144
 - leukocyte count, 143, 145
 - lung edema, 144
 - α_2 -macroglobulin, 142, 143, 145
 - platelets, 144
 - prokallikrein, 142, 143, 145
- Chemiluminescence
 - neutrophils, alveolar cell reactions, post-traumatic lung failure and ARDS, 510–511
 - oxygen free radicals, LPS generation,
 - blood, 420–422
 - lucigenin, 420, 422, 425
 - luminol, 420–424
 - superoxide radical, 422
 - Chemotaxis and thrombin, lung microvascular injury, 33
 - Chromatography, HPLC
 - leukotriene generation, polytrauma patients with ARDS, 312–313
 - lipid peroxidation products, cytotoxic, rat liver microsomes, 246–247
 - and phospholipid lung profile, ARDS, 517–521
 - reverse phase, inotropic LMW plasma substances, prolonged shock, 594
 - Chromogenic substrates, 185, 186, 191, 213–215
 - Chronotropic effects, myocardial dysfunction in sepsis, 576–578
 - Cirrhosis, 365
 - Clinical trial, PGE₁ administration in ARDS, 361–366
 - Coagulation
 - activation, catecholamines, multiple trauma, and ARDS, 477, 479–481, 485–486
 - DIC, 59
 - MOF, 460, 462
 - protease inhibitors in endotoxemia, 153–154
 - see also* specific factors and system
 - Cobra venom, 236–240, 380
 - Colony stimulating factor, granulocyte-monocyte, 432–433
 - Complement activation, 3–7

- alveolar cell reactions, posttraumatic lung failure and ARDS, 510, 512
- arachidonic acid system activation, isolated lung, 292-293, 295
- B cell function, 5
- C3a, 3-6, 77, 78, 85, 510, 512
- C3b opsonization, 15, 20
- C5a, 3-6, 20, 22-23, 77, 80, 81, 235, 237, 238, 274
- C5-derived chemotactic activity, 236-238
- catecholamines, multiple trauma, and ARDS, 477, 478
- C1 esterase inhibitor, 4
- ETX, cause of mediator release in sepsis, 379
- granulocyte mediation of tissue injury, 20-24
 - during CPB, 77-78, 84
- inhibition, C1-esterase inhibitor and elastase release, extracorporeal circulation, 107
- macrophages, 5
- methylmethacrylate cement in hip surgery, 6
- MOF, 3, 4, 7
 - ARDS, 4, 6
- oxygen free radicals and lung injury, 235-238
- whole body inflammation, trauma patient autopsy study, 59-60
 - see also under* Ischemia
- Computers, 568
 - Apple II, 568
 - software, LAMS, 335, 337
- Contractility, 321-322, 567, 569, 574, 576, 579, 581, 584
- Corticosteroids cf. BW755C in endotoxemia, 356-357; *see also* specific steroids
- Cortisol, 467, 470
- CPAP, burn shock and resuscitation, 551
- Creatinine
 - aprotinin, very high dosage. polytrauma, 181
 - limb ischemia, C3a and C5a as mediators of inflammation, 13-15, 17
- CSF, granulocyte-monocyte, 432-433
- Cyclic AMP and cyclic GMP, transmembrane signaling perturbation, endotoxemia, rat hepatocyte, 402, 403
- Cyclooxygenase inhibition
 - BW755C in endotoxemia, 302, 327, 358
 - ibuprofen, 327-328
 - and ETX-stimulated inflammation, 334, 344
 - prostacyclin in ETX shock, 369-370
 - Cysteinyl leukotrienes, 301, 303-307, 323
 - hepatobiliary elimination inhibited by ETX, 304, 305, 307
- Degranulation, leukostasis, quantitative estimation, 48-49
- Dextran sulfate, 160-163
- Dialysis-associated neutropenia, 21
- Diarrhea, ETX shock (*E. coli*), dog model, 394, 396
- Disseminated intravascular coagulation, 59
- DNA, single strand breaks, oxidant injury to cultured cells, 256-257
- Dog model, *E. coli* endotoxin shock, 393-398
- Ebselen (selenium compound), protection vs. endotoxin shock in galactosamine-sensitized rodents, 281-287
 - eicosanoid metabolism interactions, diagram, 287
 - glutathione peroxidase, 282, 285, 286
 - hemodynamics, 282, 283
 - hepatitis, 281, 284, 285
 - leukotrienes, 281, 284-286
 - liver, 283, 284, 286
- ECG
 - antioxidant protection vs. free radical mediated myocardial injury, 635
 - Ni release, myocardial damage, 621-623, 625
- Eglin, elastase inhibitor, influence on lung edema, septic pigs, 121-124
 - antithrombin III, 122-124
 - blood pressure, 123
 - E. coli*, 121-122
 - extravascular lung water, 123
 - factor XIII, 122-124
 - α_2 -macroglobulin, 122-124
 - plasma levels and urinary excretion, 122-123
- Eicosanoids

- ibuprofen and ETX-stimulated inflammation, 334, 342, 344
- metabolism, ebselen protection vs. ETX shock in galactosamine-sensitized rodents, 287
- see also* Arachidonic acid *entries*; specific eicosanoids
 - Elastase, granulocyte
 - alveolar cell reactions, posttraumatic lung failure and ARDS, 510-513
 - aprotinin, cellular effects, 166-169
 - arachidonic acid system activation, isolated lung, 296
 - extracorporeal circulation, biochemical lung monitoring during CPB, 96, 97, 100-104
 - leukostasis, quantitative estimation, 50
 - proteinase inhibitor bioavailability, injected vs. aerosolized, 203, 207
 - release during CPB, mediator of pulmonary membrane damage, 82-83
 - see also* C1-esterase inhibitor and elastase release, extracorporeal circulation; Eglin, elastase inhibitor, influence on lung edema, septic pigs
- Elastase- α_1 -proteinase inhibitor complex, and leukocyte counts, septic pig lung, 115-118
 - ARDS, 115, 118
 - bronchial washings, 116-117
 - bronchoalveolar lavage, 115
 - E. coli*, 116-118
 - ELISA, 115-116
- Electron microscopy, Ni release and myocardial damage, 622, 625
- Electron spin, PBN, oxygen radical scavengers, 261, 262, 267, 268
 - resonance, 261, 262, 267, 268
 - trapping, 261-268
- ELISA, 115-116, 127, 130
- Endorphins, 212, 227
 - β -, 385, 389
- Endothelium/endothelial cells
 - aortic, oxidant injury, cultured cells, 254-255
 - damage after endotoxin activation, granulocyte mediation of tissue injury, 25-28
 - and platelets, 26
 - neutrophil adherence to, fibrin-neutrophil interactions, lung microvascular injury, 40
 - oxygen free radicals and lung injury, 236, 238
- Endotoxemia. *See also* BW755C (NSAID)effect on endotoxemia; Protease inhibitors in endotoxemia; Microvascular permeability, endotoxemia/septic shock; Transmembrane signaling perturbation, endotoxemia, rate hepatocyte
 - Endotoxemia, multitherapy regimen, pigs, 211-222, 227-233
 - antihistamine (promethazin), 212, 213, 222, 228
 - antiplasmin, 216, 219
 - gentamicin, 222
 - hemodynamics, 216-221, 227-233
 - arterial blood pressure, 229-230
 - cardiac output, 216-218, 229, 233
 - left ventricular stroke work, 230, 231, 233
 - mean pulmonary artery pressure, 230
 - oxygen tension/saturation, 232, 233
 - PCWP, 232
 - pulmonary vascular resistance, 218, 220, 230, 231
 - Swan-Ganz catheter, 228
 - systemic vascular resistance, 216, 218, 219, 230
 - kallikrein-kinin system activation, 212-215, 220, 221, 227
 - bradykinin, 220-221
 - ketanserin, 212, 213, 222, 228
 - methylprednisolone, 212, 213, 220-222, 228
 - naloxone, 212, 213, 227, 228
 - plasma endotoxin, chromogenic substrate measurement, 213-215
 - protease inhibitors
 - antithrombin III, 212, 213, 216, 217, 220, 221, 228
 - aprotinin, 212, 213, 220, 228
 - C1-esterase inhibitor, 212-213, 220, 221, 228
- Endotoxemia, thromboxane synthetase inhibitors, 328-329

- Endotoxin (ETX)
- endothelial damage, granulocyte mediation of tissue injury, 25–28 and platelets, 26
 - leukotrienes as mediators of shock and tissue trauma, rat, 311–316
 - MOF, wound inflammatory mediators and, 527–532, 534
 - myocardial dysfunction in sepsis, 576, 584
 - cell membrane effect, 576
 - oxygen radical scavengers, prophylaxis and treatment, 262–264
 - receptor competition, lipid X inhibition of LPS neutrophil activation, 434
 - Salmonella abortus equi*, 282
 - see also* Ebselen (selenium compound), protection vs. endotoxin shock in galactosamine-sensitized rodents; Ibuprofen effect on ETX-stimulated inflammation
- Endotoxin, cause of mediator release in sepsis, overview, 377–389
- B cells, 380
 - bolus cf. infusion of pulses, 381–384, 386, 388
 - bradykinin, 380, 385, 387, 388
 - cardiac output, 377, 381–382, 385, 387, 388
 - leukotrienes, rat, 311–316
 - lymph flow, 379, 388, 389
 - microvascular permeability, 377, 379–381, 387, 388
 - shear rate, 387–388
 - myocardial depression, 387
 - opiates, endogenous, 385, 389
 - naloxone, 385, 389
 - PMNs, 378, 379, 387, 388
 - prostacyclin, 385
 - sheep model, 378–380, 384–384
 - T cells, 380, 388
 - thromboxane, 382
 - vascular resistance
 - peripheral, 377, 381–382, 385
 - systemic, 377
- Endotoxin shock
- dog model (*E. coli*), 393–398
 - arterial pressure, systemic and pulmonary, 394, 395, 398
 - cardiac output, 393–398
 - diarrhea, 394, 396
 - fluid infusion, 394, 395, 398
 - heart rate, 394, 395
 - lactate, 394, 396, 397
 - vascular resistance, systemic, 396, 397
 - ibuprofen, increased survival, 327–330
 - see also* Prostacyclin, intravenous, in endotoxin shock, rabbit; Septic shock *entries*
- Epinephrine (adrenaline), 467, 472, 473
- catecholamines, multiple trauma, and ARDS, 478, 483–486
 - transmembrane signaling perturbation, endotoxemia, rat hepatocyte, 409–412
- Erythrocytes, catecholamines, multiple trauma, and ARDS, 479
- Escherichia coli*, 328, 402, 404, 420, 423, 447
- eglin, elastase inhibitor, and lungedema, septic pigs, 121–122
 - elastase and leukocyte counts, septic pig lung, 116–118
 - ETX shock, dog model, 393–398
 - MOF, ETX and, 528–529, 531
 - see also* C1-esterase inhibitor, early *E. coli* septicemia, pigs; Kallikrein-kinin system activation, lung, *E. coli* septic sheep
- Esterase stain, leukostasis, quantitative estimation, 45, 49
- Extracorporeal circulation
- biochemical lung monitoring during CPB, 95–104
 - apnoe, 96, 98–100, 103–104
 - elastase, granulocyte, 96, 97, 100–104
 - lysozyme, 97, 99–100, 104
 - NAG, 97–99, 101–104
 - PEEP, 96, 98, 100, 103, 104
 - vena cava superior cf. left atrium, 96–98, 101, 102, 104
 - kallikrein system activation during CPB, 87
 - MDF release during CPB, 611–619
 - see also* C1-esterase inhibitor and elastase release, extracorporeal circulation;

- Kallikrein-kinin system activation during aorto-coronary bypass (CPB)
- Extravascular lung water
 alveolar cell reactions, posttraumatic lung failure and ARDS, 510-512
 burn shock and resuscitation, 548-550
 eglin, elastase inhibitor, and lung edema, septic pigs, 123
 leukotriene generation, polytrauma patients with ARDS, 312-313
see also Microvascular permeability, endotoxemia/septic shock
- β -Factor XIIa
 C1-esterase inhibitor and elastase release, extracorporeal circulation, 108, 110
 prekallikrein activation, 93
- Factor XII (Hageman factor), 159, 162, 539, 540
- Factor XIIIf, prekallikrein activation, 93
- Factor XIII
 C1-esterase inhibitor, early *E. coli* septicemia, pigs, 142, 144
 eglin, elastase inhibitor, and lung edema, septic pigs, 122-124
- Fatoxidation, flow or catabolic phase of injury, 464, 465, 469
- Fatty acids, polyunsaturated, 245-246
 4-hydroxynonenal, 246-250
see also Arachidonic acid *entries*
- Fibrin
 catecholamines, multiple trauma, and ARDS, 480-481
 deposits, glomerular, prostacyclin in ETX shock, 371, 374, 375
- Fibrin-neutrophil interactions, lung microvascular injury, 33-41
 HETEs, 40-41
 leukotriene B₄, 40-41
 neutrophil
 adherence to endothelium, 40
 aggregation, 39
 sequestration, lung, 37-39
 permeability, increased, 34-35, 39
 protein exchange, 34, 35, 39
 pulmonary lymph flow, 34, 35, 38-40
 thrombin, 33-41
 chemotactic domain, 33
 hirudin, 39
 platelet, response, 35
- Fibrinogen, catecholamines, multiple trauma, and ARDS, 480-481
- Fibrinopeptide A, 274
- Flow phase, changes in injury, 463, 465-469
cf. starvation, 465-466
- Fluid resuscitation
 burn shock, 543, 544, 552
 ETX shock (*E. coli*), dog model, 394, 395, 398
 microvascular permeability, septic shock, 487-488, 490
- FMLP, 166-168, 429
- Free radicals. *See* Antioxidant *entries*; Lipid peroxidation *entries*; Oxygen free radicals *entries*
- Galactosamine, 301, 303, 306, 307
 -sensitized mice, lipid X inhibition of LPS neutrophil activation, 431-432
see also Ebselen (selenium compound), protection vs. endotoxin shock in galactosamine-sensitized rodents
- Gamma camera, microvascular permeability, septic shock, 487, 491
- Gastrointestinal system in MOF, 460, 532
- Gebexate mesilate, 154-155, 389
- Gentamicin, multitherapy regimen for endotoxemia, pigs, 222
- Glasgow Coma Scale, 622
- Glomerular fibrin deposits, prostacyclin in ETX shock, 371, 374, 375
- Glucose
 cardiovascular abnormalities, septic shock, 447, 449-451, 454-455
 injury *cf.* sepsis, 470-472
 ischemia, small intestine, vascular perfusion, 504-505
 oxidation, flow or catabolic phase, 464-466
- β -Glucuronidase, ETX, cause of mediator release in sepsis, 379
- Glutathione peroxidase, ebselen protection vs. ETX shock in galactosamine-sensitized rodents, 282, 285, 286
- Glutathione, reduced (GSH)

- antioxidant protection vs. free-radical mediated myocardial injury, 635-639
- oxygen radical scavengers, prophylaxis and treatment, 261
- Glycerol, injury cf. sepsis, 472, 473
- Glycogen phosphorylase *a*, transmembrane signaling perturbation, endotoxemia, rat hepatocyte, 404, 405, 411-413, 416
- Granulocytes (PMNs)
 - accumulation in myocardial shock ischemia, 63-70
 - lidocaine, 65, 67-69
 - oxygen free radicals, 64
 - reperfusion, 65-66
 - activation, 253-254, 260
 - oxygen free radicals, LPS generation, blood, 419, 422, 424, 425
 - aggregation, antioxidant drugs, 276, 278
 - aprotinin, cellulareffects, 165-171
 - arachidonic acid system activation, isolated lung, 292, 296-298
 - oxygen radicals, 296
 - burn shock and resuscitation, 539-540, 547-549
 - ETX, cause of mediator release in sepsis, 378, 379, 387, 388
 - leukotriene generation, polytrauma patients with ARDS, 311, 314-315
 - limb ischemia and inflammation, 14-15
 - aggregation, 11, 16
 - monocyte CSF, 432-433
 - whole body inflammation, trauma patient autopsy study, 55, 58
 - see also* Elastase, granulocyte; Leukocyte(s); Neutrophils
- Granulocytes, mediation of pulmonary membrane damage, 75-85
- ARDS, 75, 76, 78, 83, 84
- cardiopulmonary bypass, 76-85
 - complement activation during, 77-78, 80, 84-85
 - elastase release during, 81-83
 - intrapulmonary sequestration, 79-81, 85
 - MDA levels, 79-80
 - oxygen free radical peroxidation, 79-81, 83-84
 - post-perfusion syndrome, 75, 83, 84
 - α_1 -proteinase inhibitor, 83-84
 - whole body inflammation, 84
- Granulocytes, mediation of tissue injury, 19-28
 - activation and shock lung, 23-24
 - aggregation, 21-23
 - complement system activation, 20-24
 - endothelial damage after endotoxin activation, 25-28
 - and platelets, 26
 - free iron, 27-28
 - frustrated phagocytosis, 19-20
 - intravascular activation, 20-21
 - oxygen radicals, 26-28
 - pharmacology, 24-25
 - steroids, 24-26
 - α -1-proteinase inhibitor, 27
- GSH (reduced glutathione)
 - antioxidant protection vs. free-radical mediated myocardial injury, 635-639
 - oxygen radical scavengers, prophylaxis and treatment, 261
- Hageman factor (factor XII), 159, 162, 539, 540
- Hannover Trauma Scale, 521
- Heart
 - depressant factors, 599-603
 - acidosis, 600
 - isolated papillary muscle, 602, 603
 - leucine, 601
 - MDF, 591, 592, 596, 601-604
 - nickel, 600
 - vasopressin, 601
 - myocardial depression, physiologic-metabolic correlations, septic shock, 446, 454
 - rate
 - and atropine, in hypotensive central hypovolemia, 629-631
 - ETX shock (*E. coli*), dog model, 394-395
 - myocardial dysfunction in sepsis, 574-578, 587
 - stimulant factors in shock, 599-600, 603-607
 - catecholamines and angiotensin II, 603

- histamine, 604
- inotropic, 603, 604
- MSF, shock-induced, 604–607
- ventricular function
 - hypovolemic-traumatic shock, 561, 567
 - multitherapy regimen for endotoxemia, 230, 231, 233
 - physiologic-metabolic correlations, septic shock, 444
- see also* Cardiac output; Hemodynamics; Myocardial *entries*; Nickel release, endogenous, myocardial damage
- Heart performance evaluation, hypovolemic-traumatic shock, 561–570
 - cardiodynamics, schema, 562–563
 - closed-loop feed-back control circuits, 561, 569
 - computers, 568
 - contractility, 567, 569
 - myocardium performance, 561
 - separation of control circuits, 569
 - isolated heart-lung preparation, 569–570
 - ventricular performance, 561, 567
- Hemodialysis, MOF, 460, 461
- Hemodynamics
 - aprotinin and C1-esterase inhibitor infusion and pancreatic shock, pig, 193–195
 - arachidonic acid system activation, isolated lung, 289–298
 - PAP, 292–295
 - BW755C in endotoxemia, 356–357
 - eblesen protection vs. ETX shock in galactosamine-sensitized rodents, 282–283
 - ibuprofen, 327–328
 - kallikrein-kinin system activation, lung, *E. coli* septic sheep, 135, 137
 - MDF release during CPB, 612–616, 618–619
 - PGE₁ administration in ARDS, 363–365
 - see also* Hyperdynamic/hypermetabolic state; Trypsin-induced shock, hemodynamics and proteolysis, pigs; Vascular *entries*; under Endotoxemia, multitherapy regimen, pigs
- Hemorrhage, atropine effect on heart rate, 629, 630
- Heparin, extracorporeal circulation
 - C1-esterase inhibitor and elastase release, 108
 - kallikrein-kinin system activation during CPB, 87–89, 91
- Hepatitis, eblesen protection vs. ETX shock in galactosamine-sensitized rodents, 281, 284, 285
- Hepatocytes. *See* Transmembrane signaling perturbation, endotoxemia, rat hepatocyte
- HETE and HPETE, 40–41, 334
- Hip surgery, methylmethacrylate cement in, 6
- Hirudin and thrombin, lung microvascular injury, 39
- Histamine, 162, 212, 227
 - antihistamine in multitherapy regimen for endotoxemia, pig, 212, 213, 222, 228
 - heart stimulation, 604
 - leukotrienes and lipid mediators in ARDS pathogenesis, 318, 321, 322
- Hospital Trauma Index, 56
- HPLC. *See* Chromatography, HPLC
- 5HT. *See* Serotonin
- Hydrogen peroxide
 - injury
 - cultured cells, 253–254
 - lung, 238–249
 - myeloperoxidase, oxygen free radicals, LPS generation, blood, 422
- Hydroxyl radical, oxygen free radicals and lung injury, 238–241
 - and iron chelators, 239–240
- 4-Hydroxynonenal, lipid peroxidation products, cytotoxic, rat liver microsomes, 246, 248–250
- Hyperdynamic/hypermetabolic state
 - MOF, wound inflammatory mediators and, 525–526, 531–532
 - sepsis syndrome, 526–528, 533–534
 - myocardial dysfunction in sepsis, 574, 584, 585, 587

- physiologic-metabolic correlations, septic shock, 404–442, 454
- Hypovolemic shock. *See* Heart performance evaluation, hypovolemic-traumaticshock; Inotropic plasma substances, LMW, prolonged hypovolemic polytraumatic shock, dog
- Hypoxia, alveolar, arachidonic acid system activation, isolated lung, 294–295
- Ibuprofen, 378, 389
 - MOF, wound inflammatory mediators and, 534
 - see also* BW755C (NSAID) effect on endotoxemia
- Ibuprofen effect on ETX-stimulated inflammation, 333–344
 - arachidonic acid and eicosanoids, 334, 342, 344
 - body temperature, 340–341
 - cardiac index, 338, 340
 - cyclooxygenase inhibition, 334, 344
 - general NSAID mechanism, 334
 - lymph flow, 334, 335, 337, 344
 - microvascular permeability, 340, 342, 343
 - neutropenia, 333–334, 340
 - oxygen consumption, 337, 339–341, 344
 - plasma volume, 337
 - prophylactic/therapeutic, 335
 - pulmonary vascular tone, 336
 - systemic vascular resistance, 337, 338, 340, 344
- Immunoelectrophoresis, rocket, 177, 180
- Infant respiratory distress syndrome, 517, 521
- Inflammation, whole body
 - granulocyte mediators of pulmonary membrane damage, 84
 - trauma patient autopsy study, 55–60
 - complement, 59–60
 - liver, 58
 - MOF and ARDS, 55–60
 - organ weights, 56–60
 - PMNs, 55, 58
 - thromboplastin and DIC, 59
 - see also* BW755C (NSAID) effect on endotoxemia; Ibuprofen effect on ETX-stimulated inflammation;
- Multiple organ failure, wound inflammatory mediators: *under* Ischemia
- Inhalation injury. *See under* Burn shock and resuscitation
- Injury Severity Score, 622
 - whole body inflammation, trauma patient autopsy study, 56–57
- Inositol phospholipid turnover, transmembrane signaling perturbation, endotoxemia, rat hepatocyte, 401–404, 407–409, 416
- Inotropic plasma substances, LMW, prolonged hypovolemic polytraumatic shock, dog, 591–596
 - calcium-binding, 596
 - HPLC, reverse phase, 594
 - cf. myocardial depressant factor, 591, 592, 596
 - and papillary muscle, guinea pig bioassay, 592, 595
 - sodium chloride, 591–594
 - see also* Myocardial depressant factor
- Insulin, flow or catabolic phase, 466–469, 472
- Interleukin-1
 - changes in injury, 463, 469, 472
 - MOF, wound inflammatory mediators and, 531–534
 - protease inhibitors in endotoxemia, 150
- Interleukin-2, 447
- Intestinal ischemia, vascular perfusion, rat, 503–507
- Intravascular activation, granulocyte mediation of tissue injury, 20–21
- IP₃, transmembrane signaling perturbation, endotoxemia, rat hepatocyte, 413–415
- Iron
 - ADP-, lipid peroxidation products, cytotoxic, rat liver microsomes, 247–249
 - antioxidant drugs, 272
 - chelators, oxygen free radicals and lung injury, 239–240
 - free, granulocyte mediation of tissue injury, 27–28
- Ischemia
 - limbs, C3a and C5a as mediators of inflammation, 11–17

- ARDS, 11
 bilirubin (liver function), 11, 13–15, 17
 creatinine (kidney function), 13–15, 17
 granulocytes, 14–15
 granulocytes, aggregation, 11, 16
 oxygen radicals, 15
 platelets, 14–16
 respiratory function, 11, 13–15, 17
 myocardial shock-, granulocyte accumulation, 63–70
 reperfusion, 65–66
 -reperfusion, antioxidant protection vs. free-radical mediated myocardial injury, 634–639
 Isoproterenol, myocardial dysfunction in sepsis, 577, 578
- Kallikrein**
 aprotinin and C1-esterase inhibitor infusion and pancreatic shock, pig, 194, 196–200
 inhibition, 193, 194, 196, 197, 199
 aprotinin inhibition, very high dosage, polytrauma, 175–181
 infusion, kinin-induced pathology in ARDS development, pig, 127–130
 bolus injection cf. continuous infusion, 128–129
 trypsin-induced shock, hemodynamics and proteolysis, 185–188, 191
 inhibition, 186, 189, 191
- Kallikrein-kinin system**
 aprotinin and C1-esterase inhibitor, 159–163
 arachidonic acid system, isolated lung, 289, 291–292
 catecholamines, multiple trauma, and ARDS, 477
 inhibition, C1-esterase inhibitor and elastase release, extracorporeal circulation, 107–110, 113
 multitherapy regimen for endotoxemia, pigs, 212–215, 220–221, 227
 protease inhibitors in endotoxemia, 149, 152–153
see also specific components
- Kallikrein-kinin system activation during aorto-coronary bypass (CPB), 87–93**
 aprotinin, 87–89, 91, 93
 C1-esterase inhibitor, 89, 92, 93
 extracorporeal circulation, 87
 heparin, 87–89, 91
 kallikrein, 87–90, 92
 inhibition, 87–89, 91–93
 kininogen, HMW, 87–90
 prekallikrein, 87–90, 93
 activators, 93
- Kallikrein-kinin system activation, lung.**
E. coli septic sheep, 133–138
 antithrombin III, 134, 136–138
 bradykinin, 137–138
 hemodynamics, 135, 137
 kallikrein inhibition, 134, 136–137
 lymph flow, 134, 135, 137
 prekallikrein, 134, 136, 137
 prothrombin, 134, 136–138
- Ketanserin, multitherapy regimen for endotoxemia, pigs, 212, 213, 222, 228**
- Kidney**
 aprotinin, very high dosage, polytrauma, 180–182
 creatinine, 181
 urine output, 180–181
 function (creatinine), limb ischemia, C3a and C5a as mediators of inflammation, 13–15, 17
 glomerular fibrin deposits, prostacyclin in ETX shock, 371, 374, 375
 MOF, 460–462
- Kinin**
 aprotinin and C1-esterase inhibitor infusion and pancreatic shock, pig, 199
 -induced pathology in ARDS development, kallikrein infusion, 127–130
 inhibition, C1-esterase inhibitor and elastase release, extracorporeal circulation, 107–110, 113
see also Kallikrein-kinin entries
- Kininogen**
 aprotinin and C1-esterase inhibitor infusion and pancreatic shock, pig, 199
 ARDS, pig, 127–129

- HMW
 aprotinin and C1-esterase inhibitor, 159, 161-162
 during CPB, 87-90
- Krebs-Henseleit solution, 503-507
- Kupffer cells, 534
- Lactate
 ETX shock (*E. coli*), dog model, 394, 396, 397
 physiologic-metabolic correlations, septic shock, 446, 452
- Lactoferrin, 510
- LAMS computer software, 335, 337
- Langendorff perfused hearts, myocardial dysfunction in sepsis, 577
- Leucine, heart depressant factor, 601
- Leukocyte(s)
 BW755C in endotoxemia, 347-350, 352, 353, 357
 count, C1-esterase inhibitor, early *E. coli* septicemia, pigs, 143, 145
 prostacyclin in ETX shock, 370, 372, 375
see also Elastase- α_1 -proteinase inhibitor complex, and leukocyte counts, septic pig lung; Granulocytes *entries*; Neutrophils
- Leukocytosis, MOF, wound inflammatory mediators and, 530-531
- Leukostasis, quantitative estimation, post-traumatic lung cf. controls, 43-51
 ARDS and MOF, 50
 degranulation, 48-49
 dogs, 43-45, 50
 reinfusion, 44, 48, 50
 elastase, 50
 esterase stain, 45, 49
 human autopsy cases, 45-49
 diagnoses, 46-47
 labeling, 44, 45, 48, 50-51
- Leukotrienes
 alveolar cell reactions, posttraumatic lung failure and ARDS, 510-512
 arachidonic acid system activation, isolated lung, 291, 293, 296
 ebselen protection vs. ETX shock in galactosamine-sensitized rodents, 281, 284-286
 fibrin-neutrophil interactions, lung microvascular injury, 40-41
 MOF, wound inflammatory mediators and, 531
- Leukotrienes and lipid mediators in ARDS pathogenesis, 317-324
 and C5a, 317, 318, 320-324
 and neutrophils, 324
 and smooth muscle contraction, 321-322
 histamine, 318, 321, 322
 PAF, 317-323
 chemical structure, 318, 319, 321
 schema, 324
 vascular permeability, 320-322
- Leukotrienes as mediators of ETX shock and tissue trauma, rat, 301-307
 cysteinyl, 303-307, 323
 hepatobiliary elimination inhibited by ETX, 304-305, 307
 LPS, pathogenesis mechanism, 306-307
- Leukotrienes, generation, polytrauma patients with ARDS, 311-316
 bronchoalveolar lavage, 312-314
 extravascular lung water, 312-313
 granulocytes, 311, 314-315
 HPLC, 312, 313
 RIA, 312, 313
- Lidocaine, granulocyte accumulation in myocardial shock ischemia, 65, 67-69
- Limb ischemia. *See under* Ischemia
- Lipid(s)
 cardiovascular abnormalities, septic shock, 447, 452-455
 fat oxidation in injury, 464, 465, 469
see also Leukotrienes and lipid mediators in ARDS pathogenesis
- Lipid peroxidation, 274, 275
 antioxidant protection vs. free-radical mediated myocardial injury, 633-639
 MDA, 635, 636
 oxygen free radicals and lung injury, 239-241
- Lipid peroxidation products, cytotoxic, rat liver microsomes, 245-250
 ADP-iron, 247-249
 aldehyde, 245-248
 malondialdehyde, 247, 249

- HPLC, 246, 247
 PUFAs, 245, 246
 4-hydroxynonenal, 246, 248–250
 toxic second messengers, 249
- Lipid X inhibition of LPS neutrophil activation, 427–434
 ETX receptor competition, 434
 galactosamine-sensitized mice, 431–432
 lungs, 431, 433
 cf. other lipid A monosaccharide derivatives, 427, 429, 430, 432
 oxygen free radicals, 427, 432
 superoxide, 427–429, 431
- Lipopolysaccharide, 378, 380, 385, 387, 389
 leukotrienes as mediators of ETX shock and tissue trauma, 306–307
see also Lipid X inhibition of LPS neutrophil activation; Oxygen free radicals, LPS generation, fresh human blood
- Lipoxygenase inhibition, BW755C in endotoxemia, 302, 347, 358
- Liver
 cirrhosis, PGE₁ administration in ARDS, 365
 cysteinyl leukotriene elimination inhibited by ETX, 304, 305, 307
 ebselen protection vs. ETX shock in galactosamine-sensitized rodents
 enzymes, 283, 284, 286
 toxicity, 284
 function, limb ischemia, C3a and C5a as mediators of inflammation, 11, 13–15, 17
 MOF, 460, 462
 Kupffer cell, 534
 wound inflammatory mediators and, 534
 whole body inflammation, trauma patient autopsy study, 58
see also Lipid peroxidation products, cytotoxic, rat liver microsomes; Transmembrane signaling perturbation, endotoxemia, rat hepatocyte
- Lucigenin, oxygen free radicals, LPS generation, blood, 420, 422, 425
- Luminol, oxygen free radicals, LPS generation, blood, 420–424
- Lungs
 aprotinin, very high dosage, polytrauma, 180, 182
 biochemical monitoring during CPB, 95–104
 infant RDS, 517, 521
 lipid X inhibition of LPS neutrophil activation, 431, 433
 MOF, 460–462
 phospholipid profile, ARDS in polytrauma patients, 517–521
 postperfusion, 100, 102, 104
 surfactant
 ARDS, 517, 520
 phospholipids, burn shock and resuscitation, 550–551
 ventilatory management, 455, 551
see also Alveolar *entries*; Arachidonic acid system activation, isolated rabbit lung; ARDS (adult respiratory distress syndrome); Eglin, elastase inhibitor, influence on lung edema, septic pigs; Elastase- α_1 -proteinase inhibitor complex, and leukocyte counts, septic pig lung; Fibrin-neutrophil interactions, lung microvascular injury; Granulocytes, mediation of pulmonary membrane damage; Leukostasis, quantitative estimation, posttraumatic lung cf. controls; Oxygen free radicals and lung injury, rat; Pulmonary *entries*; Respiratory *entries*
- Lymph flow
 BW755C in endotoxemia, 347, 349, 353–355, 357
 ETX, cause of mediator release in sepsis, 379, 388, 389
 ibuprofen and ETX-stimulated inflammation, 334, 335, 337, 344
 kallikrein-kinin system activation, lung, *E. coli* septic sheep, 134, 135, 137
 microvascular permeability, septic shock, 490
 MOF, wound inflammatory mediators and, 531

- pulmonary, fibrin–neutrophil interactions, lung microvascular injury, 34, 35, 38–40
- Lysophosphatidylcholine, ARDS in polytrauma, 519–521
- Lysosomal enzymes, extracorporeal circulation, biochemical lung monitoring during CPB, 95, 96, 102–103
- lysozyme, 97, 99–100, 104
- NAG, 97–99, 101–104
- see also* Elastase, granulocyte
- Lysozyme, 97, 99–100, 104
- Macaca mulatta*, 115
- α_2 -Macroglobulin, 92, 199
- binding, trypsin-induced shock, hemodynamics and proteolysis, 191
- C1-esterase inhibitor, early *E. coli* septicemia, pigs, 142, 143, 145
- eglin, elastase inhibitor, and lung edema, septic pigs, 122–124
- protease inhibitors in endotoxemia, 151
- Macrophage(s)
- and complement in shock, 5
- like cell line P388D₁, oxidant injury, 254–256
- myocardial dysfunction in sepsis, 587
- Malondialdehyde (MDA)
- antioxidant protection vs. free radical-mediated myocardial injury, 635–636
- formation, and antioxidant drugs, 276, 278
- granulocyte mediators of pulmonary membrane damage, CPB, 79–80
- rat liver microsomes, 247, 249
- Membrane
- damage. *See* Granulocytes, mediation of pulmonary membrane damage; Lipid peroxidation *entries*
- stabilization, ibuprofen, 329
- Mercaptopropionylglycine, 276
- Mesenteric artery, superior, ischemic small intestine, vascular perfusion, 503
- Metabolic control changes in injury, 463–474
- flow or catabolic phase, 463, 465–469
- cf. starvation, 465–466
- cf. sepsis, 465, 469–472
- see also* Hypodynamic/hypermatabolic state; Septic shock, physiologic and metabolic correlations, humans
- Methylmethacrylate cement in hip surgery, 6
- Methylprednisolone
- MDF release during CPB, 611, 613–615, 617–618
- multitherapy regimen for endotoxemia, pigs, 212, 213, 220–222, 228
- cf. PBN, oxygen radical scavengers, prophylaxis and treatment, 263, 268
- Microsomes. *See* Lipid peroxidation products, cytotoxic, rat liver microsomes
- Microvascular injury. *See* Fibrin–neutrophil interactions, lung microvascular injury
- Microvascular permeability, endotoxemia/septic shock, 347–352, 357, 487–491
- albumin flux, labeled, *E. coli* septic shock, 490–491
- ARDS, 487
- BW755C, 348, 354, 357
- ETX, cause of mediator release in sepsis, 377, 379–381, 387, 388
- shear rate, 387–388
- fluid resuscitation, 487–488, 490
- gamma camera, 487, 491
- ibuprofen and ETX-stimulated inflammation, 340, 342, 343
- leukotrienes and lipid mediators in ARDS, 320–322
- lymph flow, 490
- plasma volume, 489–490
- protease inhibitors, 150–151
- transcapillary escape rate, 489
- Mitochondria, 253, 260, 267
- MOF. *See* Multiple organ failure *entries*
- Monitoring. *See under* Extracorporeal circulation
- Mortality, Ni release, myocardial damage, 623
- α -MPG, 276
- MTDQ-DA, 633, 636, 639
- Multiple organ failure (MOF, MSOF)
- and complement in shock, 3, 4, 7
- ARDS, 4, 6
- leukostasis, quantitative estimation, 50

- physiologic-metabolic correlations, septic shock, 442, 443, 451, 455
- septic patients, 459-462
- whole body inflammation, trauma patient autopsy study, 55-60
- Multiple organ failure, wound inflammatory mediators, 525-535
- ARDS, 534
- burns, 525, 526, 528, 532
 - infected cf. uninfected, 527
- ETX, 527-532, 534
 - GI permeability, 532
 - prostaglandins, 529-530, 532, 534, 535
 - recurrent low-dose endotoxemia, hemodynamics, 528-529, 531
 - thromboxanes, 529-531
- hyperdynamic, hypermetabolic state, 525-526, 531-532
 - sepsis syndrome, 526-528, 533-534
- interleukin-1, 531-534
- leukocytosis, 530-531
- leukotrienes, 531
- liver, 534
- lymph flow, 531
- mediators listed, 527
- oxygen consumption, 525-527, 532
- prevention, 534-535
 - ibuprofen, 534
- sheep, 527, 531
- Multiple trauma. *See* Aprotinin, very high dosage, polytrauma; Catecholamines, multiple trauma, and ARDS; Inotropic plasma substances, LMW, prolonged hypovolemic polytraumatic shock, dog; Leukotrienes, generation, polytrauma patients with ARDS; Phospholipid lung profile, ARDS in polytrauma patients
- Multitherapy regimen. *See* Endotoxemia, multitherapy regimen, pigs
- Muscle
 - papillary, 592, 595, 602, 603
 - PO₂, oxygen and blood flow, regional differences in early sepsis, 495, 496, 501
 - skeletal, cardiovascular abnormalities, septic shock, 447-449
 - smooth, contraction, leukotrienes and lipid mediators in ARDS pathogenesis, 321-322
 - see also* Myocardial entries
- Myeloperoxidase, 422, 510
- Myocardial depressant factor, 591, 592, 596, 601-604
 - inotropic, 602
 - release during CPB, 611-619
 - aprotinin effect, 611, 613-615, 617-618
 - effects, 616-617
 - hemodynamics, 612-616, 618-619
 - methylprednisolone effect, 611, 613-615, 617-618
 - postperfusion syndrome, 616
- Myocardial dysfunction in sepsis, rat, 573-587
 - β -adrenergic stimulation, 576-577
 - isoproterenol, 577-578
 - calcium homeostasis, altered, 579, 581, 583, 584, 587
 - cardiac output, 575, 579, 584
 - chronotropic effects, 576-578
 - contractility, 574, 576, 579, 581, 584
 - endotoxin, 387, 576, 584
 - cell membrane effect, 576
 - heart rate, 574-578, 587
 - hyperdynamic, hypermetabolic state, 574, 584, 585, 587
 - Langendorff perfused hearts, 577
 - left atrial filling pressure, 580
 - macrophage, 587
 - oxygen consumption, 579, 585, 586
 - phosphate inadequacy, 579, 585
 - physiologic-metabolic correlations, septic shock, 446, 454
 - stroke volume, 574-576
 - ventricular performance, 573, 577, 579, 581, 582
 - compliance, 581
 - see also* Antioxidant protection vs. free radical mediated myocardial injury, dogs; Nickel release, endogenous, myocardial damage; *under* Granulocytes (PMNs)
- Myocardial performance, hypovolemic-traumatic shock, 561

- Myocardial stimulation factor, shock-induced, 604–607
- NAD, 255–257
- NADPH oxidase, 253, 260
- Naja naja cobra*, 236–240
- Naloxone, 212, 213, 227, 228, 385, 389
- Neutropenia
 - dialysis-associated, 21
 - ibuprofen and ETX-stimulated inflammation, 333–334, 340
- Neutrophils
 - chemiluminescence, alveolar cell reactions, posttraumatic lung failure and ARDS, 510–511
 - leukotrienes and lipid mediators in ARDS pathogenesis, 324
 - oxygen free radicals and lung injury, 235–239
 - proteinase release, 238–239
 - α_1 -proteinase inhibitor bioavailability, injected vs. aerosolized, 203–204
 - see also* Fibrin–neutrophil interactions, lung microvascular injury; Granulocytes *entries*; Lipid X inhibition of LPS neutrophil activation
- Nickel release, endogenous, myocardial damage, 600, 621–626
 - burns, 622
 - cause of death, 623
 - ECG records, 621–623, 625
 - EM, 622, 625
 - serum levels, 621, 624
- Nitrogen loss, flow or catabolic phase, 465–469
- No reflow phenomenon, 63
- Norepinephrine, multiple trauma, and ARDS, 478, 483–486
- NSAID mechanism, 334; *see also* BW755C (NSAID) effect on endotoxemia; Ibuprofen *entries*
- Opiates, endogenous (endorphins), 212, 227, 385, 389
- Organ failure. *See* Multiple organ failure *entries*
- Organ weights, whole body inflammation, trauma patient autopsy study, 56–60
- Ouabain, 581, 583
- Oxidant injury of cultured cells, 253–258
 - ARDS, 253
 - and ATP content, 254
 - bovine aortic endothelial cells, 254–255
 - DNA, SSB, 256–257
 - H₂O₂, 253–254
 - mouse macrophage-like cell line P388D₁, 254–256
 - and NAD content, 255–257
 - poly-ADP-ribose polymerase, 255–257
 - Oxidative inactivation, α_1 -proteinase inhibitor, injected vs. aerosolized, 203–204
- Oxygen
 - consumption, 337, 339–341, 344, 500
 - MOF, wound inflammatory mediators and, 525–527, 532
 - myocardial dysfunction in sepsis, 579, 585, 586
 - physiologic–metabolic correlations, septic shock, 444, 454
 - delivery and consumption, PGE₁ administration in ARDS, 361, 364–367
 - pressure
 - alveolo-arterial difference (AaDO₂), posttraumatic lung failure and ARDS, 510
 - partial, 495–497, 501, 504–505
 - tension/saturation, multitherapy regimen for endotoxemia, 232, 233
- Oxygen and blood flow, regional differences, early sepsis, 495–502
 - arterial blood pressure, 501
 - arterial oxygen transport, 499
 - cardiac output, 496, 498
 - maldistribution, 501–502
 - PO₂, 495–497
 - muscle, 495–496, 501
- Oxygen free radicals
 - arachidonic acid system activation, isolated lung, 296
 - ETX, cause of mediator release in sepsis, 379, 380
 - granulocyte
 - accumulation in myocardial shock ischemia, 64
 - mediation of tissue injury, 26–28
 - limb ischemia, C3a and C5a as mediators of inflammation, 15

- lipid X inhibition of LPS neutrophil activation, 427, 432
- peroxidation, granulocyte mediators of pulmonary membrane damage, CPB, 79–81, 83, 84
 - MDA levels, 79–80
- protease inhibitors in endotoxemia, 150–151
 - see also* Lipid peroxidation *entries*; Oxidant injury of cultured cells
- Oxygen free radicals and lung injury, rat, 235–241
 - catalase, 238, 240, 272, 274
 - cobra venom factor, 236–240
 - complement, 235–238
 - endothelial cells, 236, 238
 - H₂O₂, 238–239
 - hydroxyl radical, 238–241
 - and iron chelators, 239–240
 - lipid peroxidation, 239–241
 - neutrophils, 235–239
 - proteinase release, 328–239
 - platelets, 235–236
 - SOD, 238, 272, 274
 - superoxide radical, 238–239
- Oxygen free radicals, LPS generation, fresh human blood, 419–425
 - chemiluminescence, 420–422
 - lucigenin, 420, 422, 425
 - luminol, 420–424
 - superoxide radical, 422
 - PMN activation, 419, 422, 424, 425
- Oxygen free radical scavengers, prophylaxis and treatment of experimental shock, rat, 259–268
 - ETX, 262–264
 - PBN, 261–268
 - electron spin reponse, 261, 262, 267–268
 - cf.* methylprednisolone, 263, 268
 - reduced glutathione, α -tocopherol, SOD, 261
 - SMAO, 262–264
 - trauma, 262–267
 - see also* Antioxidant *entries*
- PAF, 317–323
 - chemical structure, 318, 319, 321
- Pancreatitis, 127, 128, 130
 - MOF, 461
 - see also* Aprotinin and C1-esterase inhibitor infusion and pancreatic shock, pig
- Papillary muscle, 595, 595, 602, 603
- Parenteral nutrition, injury *cf.* sepsis, 470
- Partial oxygen pressure (PO₂)
 - ischemia, small intestine, vascular perfusion, 504–505
 - regional differences in early sepsis, 495–497
 - muscle, 495, 496, 501
- PBN, oxygen radical scavenger, prophylaxis and treatment, 261–268
- PEEP, burn shock and resuscitation, 551
- Permeability, GI, MOF, 532; *see also* Microvascular permeability, endotoxemia/septic shock
- Peroxidation, lipid. *See* Lipid peroxidation *entries*
- pH
 - heart depressant factor, acidosis, 600
 - ischemia, small intestine, vascular perfusion, 504–505
- Phagocytosis
 - aprotinin, cellular effects, 169, 171
 - frustrated, granulocyte mediation of tissue injury, 19–20
- Phenyl-t-butyl-nitron (PBN), oxygen radical scavenger, prophylaxis and treatment, 261–268
- Phosphate inadequacy, myocardial dysfunction in sepsis, 579, 585
- Phosphatidic acid
 - ARDS in polytrauma, 519, 521
 - transmembrane signaling perturbation, endotoxemia, rat hepatocyte, 402, 404, 408
- Phosphatidylcholine, phosphatidylethanolamine, 519–521
- Phosphatidylglycerol, 517–521
- Phosphatidylinositol
 - ARDS in polytrauma, 517, 519–521
 - transmembrane signaling perturbation, endotoxemia, rat hepatocyte, 402–404, 408, 409, 416
- Phosphatidylserine, 519, 521
- Phospholipase

- Respiratory quotient, flow or catabolic phase, 464, 465
- Salmonella*
abortus equi, 282, 421, 423
minnesota, 301, 303
- Scavengers. *See* Antioxidant *entries*; Oxygen free radical scavengers, prophylaxis and treatment of experimental shock, rat
- Second messengers, toxic, lipid peroxidation products, 249
- Selenium. *See* Ebselen (selenium compound), protection vs. endotoxin shock in galactosamine-sensitized rodents
- Sepsis/septicemia
 cf. changes in injury, 465, 467–472
 multiple organ failure, 459–462
 syndrome, MOF, wound inflammatory mediators and, 526–528, 533–534
see also C1-esterase inhibitor, early *E. coli* septicemia, pigs; Eglin, elastase inhibitor, influence on lungedema, septic pigs; Elastase- α_1 -proteinase inhibitor complex, and leukocyte counts, septic pig lung; Kallikrein-kinin system activation, lung, *E. coli* septic sheep; Microvascular permeability, endotoxemia/septic shock; Myocardial dysfunction in sepsis, rat; Oxygen and blood flow, regional differences, early sepsis; Prostaglandin E₁ administration in ARDS, septic and post-surgery patients
- Septic shock, ibuprofen, increased survival, 327–330
- Septic shock, physiologic and metabolic correlations, humans, 439–456
 A–D states, 446
 ARDS, 441, 446
 cardiac abnormalities, metabolic basis, 446–453, 455–456
 hemodynamics, 440–442, 454
 cardiac output, 440–442
 vascular tone, 442, 444
 lactate, 446, 452
 MOF, 442, 443, 451, 455
 protease inhibitors, 453
 protein reprioritization, 453–454
 myocardial depression, 446, 454
 patterns of sepsis, cf. reference control state, 443–446
 oxygen consumption, 444, 454
 ventricular function, 444
 therapy, 454–456
 ventilatory management, 455
see also Endotoxin shock
- Serotonin (5HT), 162, 212, 227
 antagonist ketanserin, 212, 213, 222, 228
- Signaling. *See* Transmembrane signaling perturbation, endotoxemia, rathepatocyte
- Simplified Acute Physiologic Score, 622
- Small intestine, ischemia, vascular perfusion, 503–507
- SMAO, oxygen radical scavengers, prophylaxis and treatment, 262–264
- Sodium chloride, 591–594
- Sphingomyelin, ARDS in polytrauma, 519–521
- Spin resonance, oxygen radical scavengers, prophylaxis and treatment, 261, 262, 267, 268
- Staphylococcal α -toxin, 295–296
- Starvation cf. flow or catabolic phase of injury, 465–466
- Steroids, granulocyte mediation of tissue injury, 24–26; *see also* specific steroids
- Superoxide dismutase (SOD), 428, 429
 antioxidant protection vs. free radical mediated
 myocardial injury, 635–639
 aprotinin, cellular effects, 166
 and lung injury, 238, 272, 274
 prophylaxis/treatment, 261
- Superoxide radical
 aprotinin, cellular effects, 165, 166, 169
 lipid X inhibition of LPS neutrophil activation, 427–429, 431
 LPS generation, blood, 422
 and lung injury, 238–239
see also Oxygen free radicals *entries*
- Surgery, hip, 6; *see also* Prostaglandin E₁ administration in ARDS, septic and post-surgery patients

Survival

- aprotinin and C1 esterase inhibitor infusion and pancreatic shock, pig, 193
- ibuprofen increases, 327-330

T cells, 380, 388

Temperature, body. *See* Body temperature

Thrombin

- catecholamines, multiple trauma, and ARDS, 479, 480, 485, 486
- and fibrin-neutrophil interactions, lung microvascular injury, 33-41

Thromboplastin, 59

Thromboxanes, 305, 307

- arachidonic acid system activation, isolated lung, 291, 293-297
- burn shock and resuscitation, 541, 548
- BW755C in endotoxemia, 347, 350, 352, 355-357
- ETX, cause of mediator release in sepsis, 382
- MOF, ETX and, 529-531
- prostacyclin in ETX shock, 369-375

Thromboxane synthetase inhibitors, rat ETX, 328-329

TNF, 469, 472

 α -Tocopherol, 261, 272, 276

Transferrin, 272, 274

Transmembrane signaling perturbation, endotoxemia, rat hepatocyte, 401-416

- α_1 -adrenergic receptors, 406-407, 415
- Ca^{2+} , 401-405, 409-410, 413-416
- IP₃-stimulated release, 413-415
- Quin-2 measurement, 405

cAMP, 402

cGMP, 402-403

epinephrine, 409-412

glycogen phosphorylase α , 404, 405, 411-413, 416

inositol phospholipid turnover, 401-404, 407-409

phosphatidic acid, 402, 404, 408

phosphatidylinositol, 402-404, 408-409, 416

PIP and PIP₂, 404, 407-409, 414

protein kinase C, 403

phospholipase C, 404, 407

vasopressin, 402, 404, 407-412, 415

receptors, 405-406, 415

Trauma. *See* Heart performance evaluation, hypovolemic-traumatic shock; Leukostasis, quantitative estimation, post-traumatic lung cf. controls; Leukotrienes as mediators of ETX shock and tissue trauma, rat; Multiple trauma; *under* Inflammation, whole body

Trauma scores, catecholamines, and ARDS, 478, 480, 484

Triglyceride abnormalities, septic shock, 447, 452-455

Trypsin-induced shock, hemodynamics and proteolysis, pigs, 185-192

blood pressure (MAP), 189-191

cardiac output, 189-191

chromogenic peptide substrate analysis, 185, 186, 191

kallikrein, 185-188, 191

inhibition, 186, 188, 191

α_2 -macroglobulin binding, 191

prekallikrein, 186, 188

trypsin, plasma activity, 186, 187

vascular resistance, systemic, 190-191

Tyrosine, 442

Urinary excretion

eglin, septic pigs, 122-123

very high dosage aprotinin, polytrauma, 180-181

Vagal activity, atropine effect on heart rate, 629, 631

Vascular perfusion, intestinal ischemia, rat, 503-507

Vascular permeability. *See* Microvascular permeability, endotoxemia/septic shock

Vascular resistance

ETX, cause of mediator release in sepsis peripheral, 377, 381, 382, 385

systemic, 377

ibuprofen and ETX-stimulated inflammation, 337, 338, 340, 344

multitherapy regimen for endotoxemia, hemodynamics, 216, 218, 219, 230

pulmonary

- multitherapy regimen for endotoxemia, hemodynamics, 218, 220, 230, 231
- PGE1 administration in ARDS, 363, 365-367
- systemic, ETX shock (*E. coli*), dog model, 396, 397
- trypsin-induced shock, hemodynamics and proteolysis, 190, 191
- Vascular tone, physiologic-metabolic correlations, septic shock, 442, 444
- Vasopressin, 382, 601
 - transmembrane signaling perturbation, endotoxemia, rat hepatocyte, 402, 404, 407-412, 415
 - receptors, 405-406, 415
- Vena cava superior, lung monitoring during CPB, 96-98, 101, 102, 104
- Ventilatory management
 - inhalation injury, burn shock and resuscitation, 551
 - physiologic-metabolic correlations, septic shock, 455
- Ventricular performance
 - hypovolemic-traumatic shock, 561, 567
 - multitherapy regimen for endotoxemia, 230, 231, 233
 - myocardial dysfunction in sepsis, 573, 577, 579, 581, 582
 - compliance, 581
 - physiologic-metabolic correlations in septic shock, 444
- Verapamil, 581, 583, 584
 - burn shock and resuscitation, 542
- White blood cells. *See* Leukocyte(s); specific types
- Wound. *See* Multiple organ failure, wound inflammatory mediators
- Xanthine oxidase, 260
- ZAP, 166-168

