Leopoldina
Nationale Akademie
der Wissenschaften

NOVA ACTA LEOPOLDINA

Neue Folge | Nummer 421

The Evolution of Intensive Care Medicine

Claudia Spies and Gunnar Lachmann (Eds.)

Deutsche Akademie der Naturforscher Leopoldina –
Nationale Akademie der Wissenschaften, Halle (Saale) 2018

Wissenschaftliche Verlagsgesellschaft Stuttgart

NOVA ACTA LEOPOLDINA

Abhandlungen der Deutschen Akademie der Naturforscher Leopoldina

Herausgegeben von Jörg HACKER, Präsident der Akademie

NEUE FOLGE NUMMER 421

The Evolution of Intensive Care Medicine

Leopoldina Symposium

Berlin

February 24th and 25th, 2017

Editors:

Claudia SPIES (Berlin)
Member of the Leopoldina

Gunnar LACHMANN (Berlin)

Deutsche Akademie der Naturforscher Leopoldina –
Nationale Akademie der Wissenschaften, Halle (Saale) 2018
Wissenschaftliche Verlagsgesellschaft Stuttgart

Redaktion: Dr. Michael Kaasch und Dr. Joachim Kaasch

Die Schriftenreihe Nova Acta Leopoldina erscheint bei der Wissenschaftlichen Verlagsgesellschaft Stuttgart, Birkenwaldstraße 44, 70191 Stuttgart, Bundesrepublik Deutschland.

Die Schriftenreihe wird gefördert durch das Bundesministerium für Bildung und Forschung sowie das Ministerium für Wirtschaft, Wissenschaft und Digitalisierung des Landes Sachsen-Anhalt.

Einbandbild:
Eric Leupolt: Leopoldina-Symposium 2017 – The Evolution of Intensive Care Medicine. Das Nutzungsrecht besteht ausschließlich im Rahmen des Leopoldina-Symposiums 2017.

Bibliografische Information der Deutschen Nationalbibliothek
Die Deutsche Nationalbibliothek verzeichnet diese Publikation in der Deutschen Nationalbibliografie; detaillierte bibliografische Daten sind im Internet über http//portal.dnb.de abrufbar.

Die Abkürzung ML hinter dem Namen der Autoren steht für Mitglied der Deutschen Akademie der Naturforscher Leopoldina – Nationale Akademie der Wissenschaften.

Postadresse: Jägerberg 1, 06108 Halle (Saale), Postfachadresse: 110543, 06019 Halle (Saale)
Hausadresse der Redaktion: Emil-Abderhalden-Straße 37, 06108 Halle (Saale)
Tel.: +49 345 47239134, Fax: +49 345 47239139
Herausgeber: Prof. Dr. Dr. h. c. mult. Jörg Hacker, Präsident der Deutschen Akademie der Naturforscher Leopoldina – Nationale Akademie der Wissenschaften
Printed in Germany 2018
Gesamtherstellung: Druck-Zuck GmbH Halle (Saale)
ISBN: 978-3-8047-3849-2
ISSN: 0369-5034
Gedruckt auf chlorfrei gebleichtem Papier.

Contents

Welcome Addresses and Greetings

Ganten, Detlev: Welcome (Chairman, Scientific Commission on Health at the Leopoldina) 11

Spies, Claudia: Welcome (Chair of the Symposium) 13

Kesecioglu, Jozef: Welcome Address (President-Elect, European Society of Intensive Care Medicine) 15

Schwab, Stefan, and Waydhas, Christian: Greeting (President and Speaker, German Interdisciplinary Association for Intensive Care and Emergency Medicine [DIVI]) 17

Zwissler, Bernhard: Greeting (President, German Society of Anesthesiology and Intensive Care Medicine [DGAI]) 19

Ullrich, Lothar: Greeting (First Chairman, German Society of Specialist Nursing and Functional Services [DGF]) 21

Jonitz, Günther: Greeting (President, Berlin Chamber of Physicians) 23

Czaja, Mario: Greeting (Former Senator for Health and Social Affairs) 25

Current Perspectives and Future Innovations in Intensive Care Medicine

Lachmann, Gunnar, Weiss, Björn, Mörgeli, Rudolf, Wolf, Alissa, and Spies, Claudia: The Evolution of Intensive Care Medicine: From Recumbency to Fully Functioning in Every Day Life 29

Niehaus, Jochen, and Ganten, Detlev: Health and Critical Illness from a Global Perspective 33

Denke, Claudia: Surviving Critical Illness: A Patient's Interview 39

Intensive Care 2017: A High Price for Everyone

Brummel, Nathan: After Struggling with Death: What Price Does the Patient Pay for Survival? 47

Wunsch, Hannah: What is PICS from a Public Health Point of View? 49

Müller-Werdan, Ursula: Regaining Strength after the ICU 51

Flaatten, Hans: Multisystem Organ Failure: Why Doctors Look at the Wrong Organs ... 53

Innovations and Basic Conditions

Kesecioglu, Jozef: What's the Personal Price for Innovation? Looking Back on 10 Years of Enforcing and Managing a New ICU Concept 61

Busse, Reinhard: An Economic Analysis of Intensive Care and the Time After Survival: It May Not Be Cost-Effective to Save at the Wrong End 65

Willemeit, Thomas: Designing a Healing Environment: What's Personal and Public Investment 69

Chiche, Jean-Daniel: Life-Priority 75

Sleep Function and Dysfunction

Luetz, Alawi: Prevention of Delirium by a Modification in ICU Environment 81

Pisani, Margaret: Delirium and Circadian Integrity 85

Hatta, Kotaro: Melatonin: Panacea or Futile Hope? 91

Shehabi, Yahya: Evidence Gap to the Ideal Patient-Centered Care 95

Reduction of Stress

Weber-Carstens, Steffen: Glucose Utilization and Critical Illness 103

Slooter, Arjen: EEG-Based Diagnostics of Delirium 107

Zeilhofer, Hanns Ulrich: $GABA_A$ Receptors: The Forgotten Target 109

Hart, Nicholas: Reducing Stress, Increasing Strength: Early Mobilization and Impact on Long-Term Outcome 115

Surviving the Intensive Care Unit

Winterer, Georg: Surgery Successful – But Patient Demented 123

Sander, Michael: Perioperative Optimization and Postoperative Outcomes: From Alpha to Omega 127

Gerrard, Nicci: How to Improve Things: A Relative's Perspective 133

Innovations in Intensive Care Medicine, Perspectives from the Industry

Raspé, Christoph: Patient-Centered Innovation in Intensive Care Medicine – Hemodynamic Monitoring (Edwards Lifesciences Services GmbH) 137

Falck, Thomas, Eerden, Jacco, and Meekes, Gaby: Patient-Centered Innovations for Intensive Care Medicine (Philips Healthcare) 143

König, Alexander: Towards a Connected Intensive Care Unit (ReActive Robotics GmbH) 149

Zivkovic, Aleksandar R., Schmidt, Karsten, and Hofer, Stefan: Point-of-Care Testing of the Serum Cholinesterase Activity. A Novel Early Indicator of the Systemic Inflammation or Yet Another Vague Sepsis Biomarker? (Dr. F. Köhler Chemie GmbH) 151

Scheier, Jörg: CytoSorb® to Counteract Excessive Hyperinflammation in Intensive Care Unit Patients (CytoSorbents Europe GmbH) 157

Strategies to Achieve Patient-Centered-Outcomes

Spies, Claudia, Lachmann, Gunnar, and Schäfer, Michael: Gaps and Evidence 163

Scientific Symposium Abstract Winner

Keller, Johannes, Jeschke, Anke, Schinke, Thorsten, and Amling, Michael: 1st Prize: Protection from Septic Shock in Mice with Genetic Inactivation of Procalcitonin 171

Grunow, Julius, Wollersheim, Tobias, Kny, Melanie, Carbon, Niklas M., Giesecke, Moritz, Birchmeier, Carmen, Fielitz, Jens, and Weber-Carstens, Steffen: 2nd Prize: Protocol Based Physiotherapy and Muscle Activating Measures Improve Skeletal Muscle Synthesis in Intensive Care Unit acquired Weakness 173

Zanders, Lukas, Kny, Melanie, McShane, Erik, Lahmann, Ines, Selbach, Matthias, Birchmeier, Carmen, and Fielitz, Jens: 3rd Prize: Muscular Glycoprotein 130 Mediates Inflammation-Induced Muscle Atrophy in Mice 177

Welcome Addresses and Greetings

Welcome
(Scientific Commission on Health at the Leopoldina)

Detlev Ganten ML (Berlin)

Chairman
and President of the World Health Summit

Dear colleagues and guests,

I would like to welcome you to the Leopoldina Symposium entitled "The Evolution of Intensive Care".

Evolution points back to the beginnings of life and the grueling fight for survival, making it a suitable title for this symposium. The Leopoldina is one of the oldest academies in the world and therefore recognizes the importance of this topic for doctors and society alike.

In a short period of only about 60 years, intensive care medicine has come a long way. The effective safeguarding of breathing and circulation, even over longer periods of time, has saved the lives of countless patients on a daily basis. Intensive care medicine assumes responsibility for these severely ill patients, whose failing organs can no longer perform their duties. Intensive care physicians monitor, support and replace central systems, such as the heart, lungs and kidneys, so that they can hopefully recover, and the patient can eventually return to "normal" stationary care. In the best case, this will also allow them to get back to leading a normal life.

Just as light passes through a magnifying glass, intensive care medicine focuses and condenses medical knowledge and skills, as it often operates at the edges of what is medically possible. People and machines must work together efficiently and in harmony, leaving only minor room for error. The myriad of technical equipment and unconscious patients connected to wires, cables and monitoring devices creates the appearance of a dehumanized, mechanical practice of medicine. However, the opposite is the case, as this is also the place where doctors fight for the lives of their patients and relatives seek hope in clarification and prognosis, which is all too often uncertain. Many battles against disease and sickness are lost and often intensive care workers are pushed to their outermost personal and physical limits.

Everything that is medically feasible is done for intensive care patients. There is a constant shift in the limit to what is humanly possible, especially in the area of intensive care. But how far can or should we go in order to save lives? How many of these patients will be able to return to a healthy life? How many survivors will lose their independence due to debilitating circumstances? How much responsibility do intensive care workers bear for the lives they save? The Leopoldina symposium is looking to confront these and other serious and far-reaching questions head-on.

Experts will discuss the price of survival, which is dearly paid by society, the health system, but above all, the patient. In this special context, the term "price" is ambiguous in several

regards. These and many other issues will be discussed within a circle of colleagues who will present intensive care medicine in the light of its evolution and technical progress. They will also focus on the importance of being aware of the consequences of one's own actions, and how to incorporate this awareness into their medical and therapeutic decisions.

I would like to wish you a thoughtful and stimulating discussion which will hopefully lead to new insights into this crucial subject for the participants of this important symposium.

Prof. Dr. Detlev Ganten
Charité – University Medicine Berlin
Charitéplatz 1
10117 Berlin
Germany
E-Mail: detlev.ganten@charite.de

Welcome

Claudia Spies ML (Berlin)

Chair of the Symposium

Dear friends and colleagues,

A cordial welcome to the Leopoldina Symposium "The Evolution of Intensive Care Medicine."

For many of us, the evolution of intensive care is linked to new technical possibilities for organ support, as well as survival even in the case of severe illness. The flip side of intensive care medicine includes long-term consequences, such as cognitive impairment and immobility, as well as dependency on social transfers and long-term care.

Did we ask our patients whether they are willing to pay this price for survival? Fried et al. published an interesting insight into the treatment preferences of severely ill patients in the *New England Journal of Medicine*: almost all patients would use intensive treatments if cognitive, mental, and physical functions were maintained.

Instead of quality of life, mobility, and functional recovery, our research and clinical practice has focused on survival, organ function and length of Intensive Care Unit (ICU) stay. What we thought were "hard outcomes" actually contradict nearly all we know about the treatment preferences of our patients.

In summary, focusing on patient-centered intensive care and avoiding long-term consequences must be an ethical value of our work. This is probably the most important step in the evolution of intensive care medicine, with inter- and intersectoral implications at an individual and public health level. The gap between what we know and what we practice is tremendous and must be reduced for the sake of our patients.

I would like to express my heartfelt thanks and my deep gratitude to the National Academy of Sciences Leopoldina for supporting this multi-professional, patient-centered event, and the Charité for hosting this vitally important meeting.

Additionally, I would like to thank the European Society of Intensive Care Medicine, the German Society for Anesthesiology and Intensive Care, the German Interdisciplinary Association for Intensive Care, as well as the German Society of Nursing and Allied Health Care Professionals for their support. I am also grateful to our industrial partners for their participation and their patient-focused exhibitions. Last but not least, my deepest thanks go to all participants and to the faculty.

I wish you a fruitful and enlightening symposium which will hopefully inspire you to make real change and to make the dream of a patient-centered outcome come true for the benefit of our patients.

Prof. Dr. Claudia Spies
Head of the Department of Anesthesiology and Intensive Care Medicine
Campus Charité Mitte and Campus Virchow-Klinikum
Charité – Universitätsmedizin Berlin
Augustenburger Platz 1
13353 Berlin
Germany
E-Mail: claudia.spies@charite.de

Welcome Address
(European Society of Intensive Care Medicine)

Jozef Kesecioglu (Utrecht, The Netherlands)

President-Elect

Dear colleagues,
ladies and gentlemen,

On behalf of the European Society of Intensive Care Medicine (ESICM), I would like to welcome you to this wonderful symposium. In recent decades, intensive care medicine has grown to assume a central role in hospitals across Europe. Through tremendous advances in instruments and techniques we have succeeded in helping many patients that, only a few years ago, would have had no chance of survival. The advancement of our discipline marks a major evolutionary step in modern medicine. But we still have further to go. In intensive care medicine, it is not enough to save just the lives of our patients – they have to emerge from our wards with a certain quality of life. Providing a patient-centered outcome – doing all we can with the long-term well-being of our patients in mind – is a key concept that not only improves the rate of survival, but also the "quality of survival".

Implementing this notion of patient care in our clinics, research and teaching institutions, as well as in politics and industry, will raise the quality of intensive care medicine to a new level. This will lead to an improved provision of care and bring patients closer to the lives they once enjoyed, free of cognitive, physical and psychosocial damage that all too often accompany "survival" and sometimes follows them for the rest of their lives.

During our symposium "The Evolution of Intensive Care" I would be delighted to discuss and address the gaps we are facing. I wish all of us a symposium with thought-provoking and promising ideas which will help us change our practices and improve the lives of our patients.

Prof. Jozef Kesecioglu, MD, PhD
Chair
Division of Anesthesiology, Intensive Care
and Emergency Medicine
University Medical Center Utrecht
Heidelberglaan 100
3584 CX Utrecht
The Netherlands
E-Mail: jkesecio@umcutrecht.nl

Greeting
(German Interdisciplinary Association for Intensive Care and Emergency Medicine [DIVI[1]])

Stefan Schwab (Erlangen)
President

Christian Waydhas (Bochum)
Speaker, Quality Management and Information Technology

The further development of intensive care medicine is a major challenge for medical research, as well as for the daily treatment of patients at the bedside. However, modern intensive care medicine cannot be reduced simply to technical developments. New ways of translating scientific knowledge into everyday practice must also be found.

These new pathways will be critical for securing the high-quality of treatment required in the ICU, especially when considering the growing patient numbers, increasingly complex clinical cases, and new therapy options. It is also becoming increasingly clear that "outcome" of intensive care patients cannot simply be reduced to "survival" as the sole parameter. Many studies in recent years underline the importance of considering the quality of life after intensive care. Terms such as "post-intensive care syndrome (PICS)" and "chronic critical illness" must be central to ICU treatment. It has been shown that such undesirable treatment consequences are, in part, due to the insufficient implementation of existing guidelines. Supporting the further implementation of these guideline-based therapies will help minimize long-term complication of ICU treatment.

How can the implementation be improved? In addition to the classical methods of knowledge transfer, such as training and further education, there is a demand for innovative, and above all, sustainable approaches.

The German Interdisciplinary Association for Intensive Care and Emergency Medicine (DIVI) has created the quality indicators in intensive medicine in 2010, which are used as an instrument with which processes in intensive care medicine can be described from a qualitative perspective.

The third edition of these quality indicators will be published this year, and they have gained considerable relevance. They are part of the Intensive Medicine Peer Review, which has become one of the most innovative methods for quality improvement in the past 10 years. Supported by the DIVI and the State Chambers of Physicians, it has become a permanent structure, defining processes in the intensive care unit in a transparent manner. A confidential

1 Deutsche Interdisziplinäre Vereinigung für Intensiv- und Notfallmedizin e. V.

exchange between colleagues is established through mutual peer visitations. Experienced intensive care physicians and nurses evaluate visit and evaluate guest ICUs based on established criteria. The strengths, weaknesses, and potential of these ICUs can thus be analyzed. This is meant to support quality improvement initiatives on these wards, and drive a continuous improvement process.

Today's symposium, presented by nationally and internationally renowned speakers and thinkers, highlights the rapid advances made in intensive care medicine, as well as the several potential improvements. It must be our constant endeavor to provide high-quality intensive care medicine for the patients entrusted to us, honoring our medical and ethical responsibilities.

Prof. Dr. med. Dr. h. c. Stefan Schwab
Universitätsklinikum Erlangen
Neurologische Klinik
Schwabachanlage 6
91054 Erlangen
Germany
E-Mail: praesident@divi.de

Prof. Dr. med. Christian Waydhas
Chirurgische Universitätsklinik und Poliklinik
Berufsgenossenschaftliches Universitätsklinikum
Bergmannsheil
Bürkle-de-la-Camp-Platz 1
44789 Bochum
Germany
E-Mail: christian.waydhas@bergmannsheil.de

Greeting
(German Society of Anesthesiology and Intensive Care Medicine [DGAI[1]])

Bernhard Zwissler ML (Munich)

President

Dear Colleagues,
Ladies and Gentleman,

On behalf of the German Society of Anesthesiology and Intensive Care Medicine (DGAI) I welcome you to the International Leopoldina Symposium on "The Evolution of Intensive Care Medicine" in Berlin. The fact, that it is the fifth Leopoldina Symposium within the last 10 years being organized mainly under the auspices and leadership of anesthesiologists, truly reflects the substantial academic activity of our discipline in this field of medicine.

While recent symposia have been dealing with important, yet circumscribed medical topics (e.g. 2008 – Preconditioning; 2011 and 2016 – Sepsis; 2014 – Postoperative cognitive dysfunction), the current meeting takes a broader perspective: the development of modern intensive care medicine. With no doubt, the fast progress within this complex medical field has been, and still is, the prerequisite for many modern therapeutic concepts, especially in the surgical scenario, and anesthesiologists have made substantial contributions to this over the last decades. Although many patients owe their lives to professional care on intensive care units around the world, many areas of uncertainty and deficits still exist, both with respect to optimal medical patient management as well as logistics and organization. It is only by knowing, where we come from, that makes it possible to know, where to go in the future. Prof. Claudia Spies and her team must, therefore, be commended having assembled proficient speakers and cutting edge scientists from all over the world in Berlin, who will share their thoughts on modern intensive care medicine with us.

1 Deutsche Gesellschaft für Anästhesiologie und Intensivmedizin e. V.

I am sure that everybody will enjoy interesting talks, a fruitful discussion and – in addition – two stimulating days in the wonderful city of Berlin!
Best regards

Prof. Dr. Bernhard Zwissler
Ludwig-Maximilians-Universität München
Klinik für Anaesthesiologie
Marchioninistraße 15
81377 München
Germany
E-Mail: direktion.anaesthesie@med.lmu.de

Greeting
(German Society of Specialist Nursing and Functional Services [DGF[1]])

Lothar Ullrich (Muenster)

First Chairman

Dear colleagues and ladies and gentlemen,

On behalf of the German Society of Specialist Nursing and Functional Services e. V. (DGF), I would like to welcome you to the 2017 Leopoldina Symposium in Berlin.

Since the turn of the century there has been a gradual realization that the care of critically ill patients is an inter-professional process. Tasks, such as spontaneous awakening and breathing trials, the assessment of pain and consciousness, weaning, and delirium detection, can be equally performed by the physician and nursing professionals. At the bedside, nurses fulfill a central role, being the primary point of contact for patients, gatekeepers for relatives, and a communication hub for all other professionals. Teams can only be successful when collaboration is effective and the quality of communication is the central mechanism. Regular feedback, mutual appreciation, joint process evaluations, and time-out for team tasks are essential.

Research on outcomes in recent years has led to a fundamental change in the provision of care in intensive care units. We no longer ask what we can do to keep our patients alive, but rather what must be done today to ensure that our patients have a better quality of life in the near future. Quality of life after intensive care has become an outcome criterion. In order to improve quality of life, "holistic" approaches are necessary, which can only be implemented in an inter-professional setting. Crucial elements include early mobilization with physiotherapists, coping support for relatives and patients, and psychosocial and post-stationary rehabilitation with follow-up teams.

1 Deutsche Gesellschaft für Fachkrankenpflege und Funktionsdienste e. V.

I would like to urge you, ladies and gentlemen, to come to Berlin. Expand your horizons and become involved in shaping the progress that will ensure the welfare of our patients.

Lothar Ullrich
Universitätsklinikum Münster
Zentralklinikum
Albert-Schweitzer-Campus 1
Gebäude: A1
Albert-Schweitzer-Straße 33
48149 Münster
Germany
E-Mail: lothar.ullrich@ukmuenster.de

Greeting
(Berlin Chamber of Physicians)

Günther Jonitz (Berlin)

President

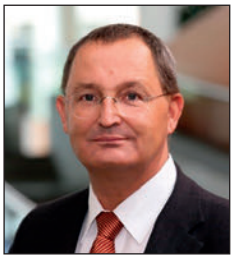

Image Credit: Kathleen Friedrich

Modern medicine is an outstanding example of successful progress. Untreatable health conditions can now be healed or at least improved, enabling patients to once again live a life of their own.

Today's medical advancements have also led to higher-risk procedures. Invasive procedures are increasingly common – not only in the surgical field, but also in fields formerly considered to be "conservative medicine", such as cardiology or neurology.

The same change is happening to our patients. Multimorbid patients who, in the past, would have been unable to survive an operation or the postoperative period – my grandmother died in a hospital because of a hip fracture that could not be operated on in the early 1970s, my grandfather refused to eat and therefore died at home one hour before his wife – can now be successfully treated to gain a few more happy years.

We can now treat higher-risk patients by performing more risky procedures, all in the hope of producing value for patients in terms of a longer or better quality of life.

But are we actually doing more good than harm? Is survival the only indicator of good quality? Would we ourselves want to undergo the same things that we subject our patients to? Is "can-do medicine" the right choice for patients or is it just good for our egos?

All these efforts come together in intensive care. Intensivists have to take care of everything that works and a lot of things that do not work. Acting as a bridge between different fields of medicine, they are ideally positioned to start a new discussion about what is right and wrong in medicine and specifically in the field of intensive care.

I congratulate the organizers for having the courage to open up this discussion and wish everyone an enriching meeting with many fruitful discussions and conclusions. It is something that our patients – and maybe we ourselves – urgently need.

Günther Jonitz, MD, PhD
President
Berlin Chamber of Physicians
Friedrichstraße 16
10969 Berlin
Germany
E-Mail: kammer@aekb.de

Greeting

Mario Czaja (Berlin)

Former Senator for Health and Social Affairs

Dear Sir or Madam,

Scientific and technical progress, coupled with the steady rise in life expectancy year on year, are placing ever greater demands on our healthcare system. What can top-level medicine do? It is torn between doing the maximum that is medically possible and doing what is ethically responsible. It is not just a matter of always putting the patient in the center of every medical and political decision, making the right decision with regard to both aspects is a difficult task for intensive care medicine.

Over 50 % of the people treated in the intensive care sector have cognitive disorders or restricted mobility. According to a current forecast, intensive care medicine in Berlin will increase by about 10 % by 2020. In the interest of the general public, it is important to reduce cognitive deficits, achieve full functional rehabilitation, and prevent psychosocial restrictions. Delirium often occurs in this context, which can be alleviated by a targeted triad of prevention, early detection and early treatment. The hospital plan has provided some improvements for these broad requirements:

– The quality of care is reinforced by the use of nursing teams in the intensive care unit which provide at least 30 % of intensive care professionals.
– The participating specialist areas must further develop interdisciplinary cooperation.
– Improvement in the supply chains between acute care and neurological (early) rehabilitation .
– In order to access the latest scientific findings in this highly demanding sector, more advanced training in intensive care medicine or other specialist training courses is called for.

Furthermore, comprehensive and innovative approaches are required as exemplified in the new intensive care unit of the Charité on the Virchow-Klinikum Campus. An even stronger focus is placed on the individual needs of the patient through new spatial design ideas for the intensive care room. This helps to relieve stress and anxiety and to improve the recovery process. This is achieved by creating more privacy between the patient and his/her family members and by reducing the amount of irritating equipment noise. The brightness and temperature can be individually adjusted by means of a modern room design. This also ensures a natural sleep-wake cycle for more efficient healing processes.

Finally, I would like to express my sincere thanks to you as you are working to improve the quality of our medical care in addition to your normal demanding working hours. I am

very pleased that you have selected Berlin as the location of your conference – certainly a good choice in view of its broad and significant achievements in health care.

In this spirit, I would like to wish you an exciting discussion and a productive symposium on "The Evolution of Intensive Care Medicine".

Mario Czaja
CDU-Fraktion
des Abgeordnetenhauses von Berlin
Preußischer Landtag
10111 Berlin
Germany
E-Mail: post@marioczaja.de

Current Perspectives and Future Innovations in Intensive Care Medicine

Nova Acta Leopoldina NF Nr. *421*, 29–31 (2018)

The Evolution of Intensive Care Medicine: From Recumbency to Fully Functioning in Every Day Life

Gunnar Lachmann, Björn Weiss, Rudolf Mörgeli, Alissa Wolf, and Claudia Spies ML (Berlin)

Abstract

The paper delivers a short introduction to the discussion on progress in intensive care medicine.

Zusammenfassung

Der Beitrag liefert eine kurze Einführung in die Diskussion über den Fortschritt in der Intensivmedizin.

Progress in intensive care medicine has significantly improved survival rates for life-threatening conditions in recent decades. Survivors, however, often suffer from significant restrictions, including cognitive impairment, mental disorders, loss of mobility and social isolation, and experience significant limitations with regard to health-related quality of life (Elliott et al. 2014, Pandharipande et al. 2014). This symptom complex is also referred to as "Post-Intensive Care Syndrome" (PICS) (Tempel and Pfeifer 2013). PICS also comprises persistent cognitive dysfunction, acquired weakness and post-traumatic stress disorder (Elliott et al. 2014). Mobility restrictions can still be detected five years after discharge (Herridge et al. 2003). In 40 % of all patients, cognitive damage still exists three months after discharge, which is still detectable in 34 % of patients after one year (Pandharipande et al. 2014). Functional restrictions ultimately affect more than half of all patients receiving intensive care (Elliott et al. 2014).

To counteract PICS, clinical trials increasingly focus on improving functional outcomes, i.e. preservation of physical and mental integrity (Schweickert et al. 2009). A milestone in this is the 2015 DAS guideline on analgesia, sedation and the management of delirium (*Taskforce DAS* et al. 2015), which is increasingly viewed as a quality indicator of German intensive care units. There are new scientific, social and economic challenges associated with the reduction in the quality of life faced by survivors of critical illness, as well as with a paradigm change in intensive care towards a conscious, cooperative patient who actively participates in the healing process. These challenges will be presented and critically analyzed with international experts as part of the *Nova Acta Leopoldina* "The Evolution of Intensive Care Medicine". However, current evidence and technical progress are not enough for patients. The quality of life after a severe illness is considerably restricted and attention and memory disturbances, as well as depression and post-traumatic stress disorder, are frequent. There is still a lack of awareness of these gaps in care in society, the economy and politics. Gaps be-

tween the ideal patient-centered state (Fig. 1) and the current state (Fig. 2) will be specified, discussed and presented as a central part of the *Nova Acta Leopoldina* "The Evolution of Intensive Care Medicine".

First, we will focus on socio-political and individual medical issues, the significance of PICS in the national and international context, as well as the adaptation of intensive care medicine necessary to meet these new challenges. Furthermore, scientific multisystem approaches

Fig. 1 Ideal patient-centered outcome

Fig. 2 Current state of patient care

for improving functional outcomes will be merged to promote an interprofessional discussion and elucidate functional outcomes with emphasis on cognition and mobility from the perspective of various disciplines and areas of research. In this high-stake area, our ultimate goal is to improve the well-being of our patients – a patient-centered outcome, in which attention is placed on the patient (Fig. 1) – by focusing on the development of science, evidence and excellence in order to meet our individual medical and social responsibilities.

References

Elliott, D., Davidson, J. E., Harvey, M. A., Bemis-Dougherty, A., Hopkins, R. O., Iwashyna, T. J., Wagner, J., Weinert, C., Wunsch, H., Bienvenu, O. J., Black, G., Brady, S., Brodsky, M. B., Deutschman, C., Doepp, D., Flatley, C., Fosnight, S., Gittler, M., Gomez, B. T., Hyzy, R., Louis, D., Mandel, R., Maxwell, C., Muldoon, S. R., Perme, C. S., Reilly, C., Robinson, M. R., Rubin, E., Schmidt, D. M., Schuller, J., Scruth, E., Siegal, E., Spill, G. R., Sprenger, S., Straumanis, J. P., Sutton, P., Swoboda, S. M., Twaddle, M. L., and Needham, D. M.: Exploring the scope of post-intensive care syndrome therapy and care: engagement of non-critical care providers and survivors in a second stakeholders meeting. Critical care medicine *42*/12, 2518–2526 (2014)

Herridge, M. S., Cheung, A. M., Tansey, C. M., Matte-Martyn, A., Diaz-Granados, N., Al-Saidi, F., Cooper, A. B., Guest, C. B., Mazer, C. D., Mehta, S., Stewart, T. E., Barr, A., Cook, D., Slutsky, A. S., and *Canadian Critical Care Trials Group*: One-year outcomes in survivors of the acute respiratory distress syndrome. The New England Journal of Medicine *348*/8, 683–693 (2003)

Pandharipande, P. P., Girard, T. D., and Ely, E. W.: Long-term cognitive impairment after critical illness. The New England Journal of Medicine *370*/2, 185–186 (2014)

Schweickert, W. D., Pohlman, M. C., Pohlman, A. S., Nigos, C., Pawlik, A. J., Esbrook, C. L., Spears, L., Miller, M., Franczyk, M., Deprizio, D., Schmidt, G. A., Bowman, A., Barr, R., McCallister, K. E., Hall, J. B., and Kress, J. P.: Early physical and occupational therapy in mechanically ventilated, critically ill patients: a randomised controlled trial. Lancet. *373*/9678, 1874–1882 (2009)

Taskforce DAS, Baron, R., Binder, A., Biniek, R., Braune, S., Buerkle, H., Dall, P., Demirakca, S., Eckardt, R., Eggers, V., Eichler, I., Fietze, I., Freys, S., Fründ, A., Garten, L., Gohrbandt, B., Harth, I., Hartl, W., Heppner, H. J., Horter, J., Huth, R., Janssens, U., Jungk, C., Kaeuper, K. M., Kessler, P., Kleinschmidt, S., Kochanek, M., Kumpf, M., Meiser, A., Mueller, A., Orth, M., Putensen, C., Roth, B., Schaefer, M., Schaefers, R., Schellongowski, P., Schindler, M., Schmitt, R., Scholz, J., Schroeder, S., Schwarzmann, G., Spies, C., Stingele, R., Tonner, P., Trieschmann, U., Tryba, M., Wappler, F., Waydhas, C., Weiss, B., and Weisshaar, G.: Evidence and consensus based guideline for the management of delirium, analgesia, and sedation in intensive care medicine. Revision 2015 (DAS-Guideline 2015) – short version. Ger. Med. Sci. 2015;13:Doc19. doi: 10.3205/000223. eCollection 2015

Tempel, M., and Pfeifer, M.: Das Post Intensive Care Syndrom – eine neue Entität? [Post intensive care syndrome – a new entity?]. Dtsch. Med. Wochenschr. *138*/23, 1221–1224 (2013)

Dr. Gunnar Lachmann
Klinik für Anästhesiologie
mit Schwerpunkt operative Intensivmedizin
Campus Charité Mitte und
Campus Virchow-Klinikum
Charité – Universitätsmedizin Berlin
Augustenburger Platz 1
13353 Berlin
Bundesrepublik Deutschland
Tel.: +49 30 450531012
Fax: +49 30 450531911
E-Mail: gunnar.lachmann@charite.de

Nova Acta Leopoldina NF Nr. *421*, 33–38 (2018)

Health and Critical Illness from a Global Perspective

Jochen Niehaus and Detlev Ganten ML (Berlin)

Abstract

According to Darwin's theory of evolution, human populations are influenced by natural selection to make them best suited to succeed in the struggle for life. Ideally, as an expression of this perfection, we should be healthy; however, in reality we are not. Cardiac and vascular diseases, mental illness, bone and joint diseases, and tumors occur so frequently that they are almost normal. We are the product of evolution and live like our ancestors but have "unnatural" preferences and values: We now live in the revolution of urban living. The occurrence of many "civilization diseases" can be explained by the gap between our biological past and cultural progress.

Doctors have been around for several thousands of years, hospitals were founded a few hundred years ago, and intensive care emerged 60 years ago. The specialty of intensive care started in the early 1950s in Copenhagen during Denmark's poliomyelitis epidemic. The emergency room was provided with equipment to treat shock and respiratory failure – a breakthrough innovation at the time. Anesthetists were urgently needed and became a permanent fixture. The temporary monitoring stations now became permanent intensive wards, because even after the epidemic, critically ill patients and patients who had been recently operated on had the best chances of survival there.

Medicine and, above all, intensive care medicine has made rapid progress in dealing with diseases and increasing healing rates, but it goes hand in hand with ever higher personnel, technical and financial costs. Health care has now become the largest economic sector in the world. The enormous use of resources has produced successful results. Never before have people lived longer and healthier lives. There have also been major advances in the diagnosis and treatment of diseases. But everything is becoming more and more complex and expensive. In wealthy countries, health systems are already at their limits.

Our social environment and financial situation, environmental pollution, climate change, the physical and geological environment and many other factors influence health and disease more than our biology and the availability of medical care. Our own behavior and lifestyle are the decisive factors that unite our innate biology and the environment in which we live or want to live. Prevention is the most important measure for improving health at a global level. Global health requires solidarity between rich and poor countries. The living conditions of the inhabitants must be improved, often starting with basic things like access to clean water, clean air and sufficient food. Education is the most important prerequisite for health.

Zusammenfassung

Nach Darwins Evolutionstheorie werden menschliche Populationen durch die natürliche Selektion so beeinflusst, dass sie erfolgreich an den Überlebenskampf angepasst sind. Idealerweise sollten wir im Ergebnis dieser Vollkommenheit gesund sein. In Wirklichkeit sind wir es jedoch nicht. Herz- und Gefäßerkrankungen, psychische Erkrankungen, Knochen- und Gelenkerkrankungen sowie Tumoren treten so häufig auf, dass sie fast normal erscheinen. Wir sind das Produkt der Evolution und leben wie unsere Vorfahren, haben aber „unnatürliche" Präferenzen und Werte: Wir leben jetzt in der Revolution des urbanen Lebens. Das Auftreten vieler „Zivilisationskrankheiten" kann durch die Kluft zwischen unserem biologischen Erbe und dem kulturellen Fortschritt erklärt werden.

Ärzte gibt es seit mehreren tausend Jahren, Krankenhäuser wurden vor einigen Hundert Jahren gegründet, und die Intensivpflege entstand vor 60 Jahren. Das Fachgebiet der Intensivpflege entwickelte sich in den frühen 1950er Jahren in Kopenhagen während der Poliomyelitis-Epidemie in Dänemark. Die Notaufnahme wurde mit Geräten zur Behandlung von Schock und Atemstillstand ausgestattet – eine bahnbrechende Innovation zu dieser Zeit. Anästhesisten wurden dringend benötigt und wurden zu einer festen Größe. Die zeitweiligen Überwachungsstationen wurden nun zu permanenten Intensivstationen, da schwerkranke Patienten, auch nach der Epidemie, und Patienten, die vor kurzem operiert wurden, dort die besten Chancen zum Überleben hatten.

Medizin, und vor allem Intensivmedizin, machte schnelle Fortschritte in der Behandlung von Erkrankungen und mit erhöhten Heilungsraten, aber all das ging mit höheren Kosten für Personal und Technik und einem höheren Finanzaufwand einher. Das Gesundheitswesen ist jetzt der größte Wirtschaftszweig der Welt geworden. Der enorme Ressourcenverbrauch führte zu erfolgreichen Ergebnissen. Niemals zuvor hatten die Menschen längere und gesündere Leben. Es gab auch große Fortschritte in der Diagnose und der Behandlung von Krankheiten. Jedoch wird alles immer komplexer und teurer. Sogar in reichen Ländern stoßen die Gesundheitssysteme bereits an ihre Grenzen.

Unser soziales Umfeld und unsere finanzielle Situation, Umweltverschmutzung, Klimawandel, physische und geologische Umwelt sowie viele andere Faktoren beeinflussen Gesundheit und Krankheit mehr als unsere Biologie und die Verfügbarkeit medizinischer Versorgung. Unser eigenes Verhalten und unser Lebensstil sind die ausschlaggebenden Faktoren, die unsere eigene Biologie und die Umwelt, in der wir leben oder leben wollen, vereinen. Prävention ist die wichtigste Maßnahme zur Gesundheitsverbesserung auf globaler Ebene. Globale Gesundheit erfordert Solidarität zwischen reichen und armen Ländern. Die Lebensbedingungen in den ärmeren Ländern müssen verbessert werden. Oft beginnt dies mit grundlegenden Dingen, wie Zugang zu sauberem Wasser, sauberer Luft und ausreichender Nahrung. Bildung ist die wichtigste Voraussetzung für Gesundheit.

1. Development of Intensive Care Medicine

Intensive care is a branch of medicine which has developed in the last 60 years. In the past, ether masks, and tongue and mouth openers were used for anesthesia as intubation anesthesia was unknown (Ibsen 1975). In some cases the few anesthetists worked in the operating rooms. There was no medical rescue and no apparatus monitoring circulatory instability. Patients with breathing difficulties were ventilated by hand and with a mask. A mammoth vacuum chamber, the iron lung, was used to perform long-term ventilation. The specialty of intensive care started in the early 1950s in Copenhagen during Denmark's poliomyelitis epidemic. When the disease broke out in 1952 there were nearly 6,000 poliomyelitis cases in the country, including 2,450 patients with respiratory paralysis. All of the severe cases were brought to Blegdams Hospital, the only hospital specializing in the treatment of transmissible diseases. At the height of the epidemic, between August and December 1952, up to 50 polio patients were admitted to the hospital every day, a dozen of whom exhibited severe bulbar symptoms. Many were already unconscious when they arrived. A young anesthetic surgeon, Björn Ibsen, decided that the hospitals referring the patients were to be provided with doctors and equipped with oxygen and suction devices. The emergency room was also provided with equipment to treat shock and respiratory failure – a breakthrough innovation at the time.

The seven existing respirators were far from sufficient in handling the flood of patients. Also, solely administering oxygen was proving to be ineffective: most respiratory patients died within a few days. Björn Ibsen suspected that hypoventilation due to higher levels of carbon dioxide in the respiratory air was the real culprit. Within a few days, tracheotomies, intubation, positive pressure ventilation, respiratory tract suction, thiopental for sedation, curare for relaxation, the monitoring of carbon dioxide absorption, and air humidifiers were introduced. As a consequence, the mortality rate fell from 92 % to 25 % (Reisner-Sénélar 2009). Three new wards with a total of 100 beds, so-called monitoring stations, were set up for the many surviving patients. Manual ventilation was carried out in six-hour shifts by 260 nurses, together with 250 physicians who had been quickly instructed in the procedure.

The cost of this care was, of course, enormous. Anesthetists were urgently needed and became a permanent fixture. The temporary monitoring stations now became permanent intensive wards, because even after the epidemic, critically ill patients and patients who had been recently operated on had the best chances of survival there. Medicine and, above all, intensive care medicine has made rapid progress in dealing with diseases and increasing healing rates,

as we have seen in the historical example above. Yet it goes hand in hand with ever higher personnel, technical and financial costs. Medics have created a new discipline with a great deal of technical equipment. This has been seized upon by many other areas of medicine and health care. In Germany, there are currently about 4.5 million employees in more than 800 health care professions. One out of ten jobs is in the health care sector, and every ninth euro of the gross domestic product is spent on it. Health care has now become the largest economic sector in the world – five times larger than the automotive industry. The enormous use of resources has produced successful results. Never before, at least in our country, have people lived longer and healthier lives. There have also been major advances in the diagnosis and treatment of diseases. But everything is becoming more and more complex and expensive, and doctors are all too often helpless. In wealthy countries, health systems are already at their limits. Poor regions cannot afford such highly developed medicine.

2. The Evolution of Humans

A better understanding of history may even help us predict the future. Doctors have been around for several thousands of years, hospitals were founded a few hundred years ago, and intensive care emerged 60 years ago. It has taken nature three and a half billion years to construct modern-day humans. Through an unimaginable number of evolutionary experiments of trial and error, our biology has been optimized to the special conditions of the earth, to its gravitation and temperature and to the mixture of elements in the water and atmosphere beginning with the first monocots, the archaebacteria. We are tailor-made for this world. Our genetic heritage is that of optimally adapted winners. According to Darwin's theory of evolution, human populations are influenced by natural selection to make them best suited to succeed in the struggle for life. Ideally, as an expression of this perfection, we should be healthy; however, in reality we are not. Cardiac and vascular diseases, mental illness, bone and joint diseases, and tumors occur so frequently that they are almost normal. Our bodies reveal their weak points, where, contrary to their construction, we strain them beyond what is tolerable. Damage to critical points is responsible for disability or death well before our lifespans reach their natural limit. Something is obviously disturbing the harmony between our biology and our environment. Something has changed in our living environment which no longer fits into our grand scheme. We are the product of evolution and live like our ancestors but have "unnatural" preferences and values: with the cellular processes of bacteria and amoeba, the spine and organs of fish, the ancient brain functions of primates, and Stone Age behavior. We now live in the revolution of urban living. The occurrence of many "civilization diseases" can be explained by the gap between our biological past and cultural progress.

There are new influences for which we are not biologically created and which make many of us sick. So-called civilization diseases affect whole segments of the population that are unable to withstand the damaging pressure from outside. We need to ask ourselves what these harmful effects are. We should identify them and, if possible, turn them off. We have to adapt better to our new circumstances, as all our ancestors have successfully done.

In recent years, evolutionary medicine has created a new science that allows us to better understand ourselves and our nature. Genetic analyses precisely describe the evolutionary steps of humans – from monocots to fish, amphibians, reptiles and primates. We now recognize much more clearly why we are sick. An important cause of so-called civilization diseas-

es, which today accounts for more than 80 % of diseases, is that we are increasingly removed from our natural living conditions. Evolution has given us old patents which now have to function in a modern, urban society. This distance between evolutionary biology and modern lifestyles, the "evolution trap", is one of the causes of cardiovascular disease, disorders of the musculoskeletal system and mental illness.

3. Health Care and the Medical Profession

Medical care that is even more complex than intensive care is not the solution to our health problems. Biology is only part of the root cause of disease. Health is much more than medicine. Medically repairing and healing sick people is expensive, not always as effective as desired and intended, and often no longer possible with the aid of therapy and medicine if the doctor is called in too late. Living conditions and the environment in all its manifestations often impact our health much more than medicine. Our social environment and financial situation, environmental pollution, climate change, the physical and geological environment and many other factors influence health and disease more than our biology and the availability of medical care.

Our own behavior and lifestyle are the decisive factors that unite our innate biology and the environment in which we live or want to live. We have to think about ourselves and about health and disease in a larger context. The civilization diseases that threaten us can only be prevented through measures that benefit everyone. Diseases begin long before the appearance of symptoms. Conversely, health begins at birth and must be promoted right from the beginning.

4. Maintaining Health

Once a patient is admitted to the intensive care unit with heart failure, a lot has already gone wrong. Have the doctors failed? Long before the infarction, cardiologists should have put in a stent or cardiac surgeons should have conducted a bypass. The General Practitioner has failed to lower blood pressure and control lipids. Perhaps more importantly, the patient has not paid enough attention to his health and has not done what is necessary and possible. Frequently: "[...] but the circumstances made it difficult [...]" for him to take responsibility for his own health.

One might think that the patient himself is responsible for his condition. He should have taken better care of himself, exercised more, and undergone preventative medical screenings. But what else can be learned from his morbid obesity?

His parents could have helped him find joy in exercising and healthy eating when it was still possible. It might be necessary to multiply cardiovascular risk factors for school or failure.

Should parents and schools blame the companies that spend billions on advertising to sell us unhealthy products high in calories? How can your health not be jeopardized by walking through streets crowded with cars and being exposed to poor air quality, or by sitting at work all day? The overall social connections are often counteractive to health. Such cases require intensive medical treatment.

5. Our Mission: Improve Health and Health Care Worldwide

Our living standards generally improved during the industrial revolution. However, these higher living standards greatly raised the risk of health problems such as a sedentary lifestyle, heart disease, obesity, back and joint pain, and other neuropsychiatric disorders including depression and dementia. Health care may provide adequate intervention, early detection, or community referral options for individuals with these diseases and behavioral or mental disorders, but there will not be a single measure that will save us – a silver bullet. Changes are necessary in many areas, and all areas of life have to be examined with regard to how they affect health. We search for small improvements everywhere: in urban development, transport, the educational system, the food industry, work and family. Health care is a significant factor driving these changes. That's why everyone has to work together to improve health.

Prevention is the most important measure for improving health at a global level. Global health requires solidarity between rich and poor countries. The living conditions of the inhabitants must be improved, often starting with basic things like access to clean water, clean air and sufficient food. To achieve this, a minimum amount of prosperity is necessary, which in turn leads to better education. Education is the most important prerequisite for health. This applies to every stage of its preservation, to the production of basic economic conditions, and to the possibility and implementation of a healthy lifestyle.

6. Improving Knowledge Faster

Much of the power of evolutionary thinking in medicine comes from its ability to foster integrative thinking about our bodies as products of evolutionary processes. The principles that underlie biological complexity, genetic diversity, interaction between the systems within the body, human development, and environmental influence guide our understanding of human health and the diagnosis and treatment of human disease. We will hopefully come to appreciate the important role a biological view of disease has in understanding human and environmental health. Thus, we can improve some of our behaviors that would nudge us in the right direction.

With the expansion of knowledge, there is a need to apply this knowledge to real-life situations in order for it to be of value. More in-depth medical knowledge, research institutions and industrial technology will make it easier to bring about mutual reinforcement, added value and impact. First and foremost, patients will benefit more quickly from medical therapies and products than ever before. The central challenges lie in accelerating research at the basic level, facilitating bench-to-bedside translation of research into medical innovation and better health care. The German Centers for Health Research have been set up to close knowledge gaps and improve prevention, diagnosis and treatment in order to achieve the highest level of therapeutic efficacy possible for each patient. This research association maintains 40 locations and more than 100 university-based and independent research partners. There is also greater involvement by private companies in this major effort. Innovative public–private partnerships and community activism have stimulated activity to develop new diagnostic, therapeutic and preventative tools to which there is more equitable and affordable access.

7. Science and Research Point the Way, But They Do Not Go Far Enough

Björn Ibsen, the notable Danish pioneer of modern intensive care medicine, became involved in the 1952 poliomyelitis outbreak in Denmark. He implemented tracheostomy and manual intermittent positive pressure ventilation to manage respiratory failure, thereby markedly decreasing mortality. We turned to mechanical ventilation once the technique was available. The permanently tetraplegic patient did not leave the hospital for seven years. The fact that the first intensive care units and entire hospitals were not filled with severe cases of polio at that time was due to the development and rapid spread of the polio vaccination two years after the Copenhagen epidemic.

We cannot hope for a similar scientific breakthrough in the field of cardiovascular or oncological diseases. The epidemics of our time, the consequences of which intensive care physicians are now fighting, include obesity, lack of exercise and stress. In order to overcome them, physicians and scientists must point the way for us. We can accomplish more as a global society. There is a growing need to enhance public awareness of the impact that science and technology have on our daily lives – including ethical, moral, legal, social and economic aspects. In recent years, advances in biotechnology and information technology have dramatically increased public interest in a wide range of areas. However, the science, research and policy in these areas must be transparent and understandable. To this end, we need to improve education and communication on these issues at all levels. We particularly need to make young people enthusiastic about the fascinating world of science and technology and promote a greater public understanding of science. This will improve our health and well-being. Intensive care medicine will need to develop further to be more effective on an individual basis.

References

Ibsen, B.: From anaesthesia to anaesthesiology. Personal experiences in Copenhagen during the past 25 years. Acta Anaesthesiologica Scandinavica Supplementum *61*,1–69 (1975)

Reisner-Sénélar, L.: Der dänische Anästhesist Björn Ibsen – ein Pionier der Langzeitbeatmung über die oberen Luftwege. Dissertation, Fachbereich Humanmedizin der Johann Wolfgang Goethe-Universität Frankfurt am Main 2009

Jochen Niehaus
Chefredakteur Focus Diabetes
und Focus Gesundheit
Arabellastraße 23
81903 München
Germany
Tel.: +49 89 92503929
Fax: +49 89 9250
E-Mail: j.niehaus@focus-magazin.de

Prof. Dr. Detlev Ganten
Charité – University Medicine Berlin
Charitéplatz 1
10117 Berlin
Germany
Tel.: +49 30 450 572101
Fax: +49 30 450 572911
E-Mail: detlev.ganten@charite.de

Nova Acta Leopoldina NF Nr. *421*, 39 – 43 (2018)

Surviving Critical Illness: A Patient's Interview

Claudia Denke (Berlin)

Abstract

Critical illness and intensive care admission are unexpected events for the majority of patients, and most of them feel a high level of physical and emotional stress during their treatment. This greatly impacts long-term outcomes. Hence, several follow up studies and interviews with patients after critical illness have shown that many survivors experience impairment in mental health, physical function and cognition known as post-intensive care syndrome (PICS). Strategies to minimize the stress level during ICU treatment and subsequent long-term impairments include cognitive stimulation, minimize sedation, early mobilization, and the presence and support of family members

Zusammenfassung

Die Mehrzahl der Patienten erleben kritische Erkrankungen und Behandlungen auf der Intensivstation völlig unerwartet. Sie empfinden daher ein hohes Maß an körperlichen und emotionalen Belastungen während ihrer Behandlung. Dies hat wiederum starken Einfluss auf das Langzeitergebnis. Eine Vielzahl von Nachuntersuchungen und Interviews mit Patienten nach schwerer Erkrankung zeigte, dass viele Überlebende unter psychischen, körperlichen und kognitiven Beeinträchtigungen leiden, dem sogenannten *Post-Intensive Care Syndrome* (PICS). Strategien, um das Stressniveau während der Behandlung zu reduzieren und somit langfristige Beeinträchtigungen zu minimieren, sind beispielsweise kognitive Stimulation, Reduktion der Sedierung, frühe Mobilisierung sowie die Anwesenheit und Unterstützung der Familie.

Critical illness is known to be highly stressful and, for many patients, is a traumatic experience (Rotondi et al. 2002). Stressors are multifactorial and result from treatment procedures, illness-related impairments, environmental factors, and associated mental stress. We present results from interviews with patients following critical illness that are in line with numerous similar investigations.

Physical stressors of illness are very frequently a result of invasive and painful procedures. Patients who were asked about their most disturbing ICU-related physical experience report the insertion of intravenous and arterial lines, injections, physical examinations and manipulations associated with pain, sleeplessness, restraints, endotracheal tube, thirst, and immobilization (Kalfon et al. 2010, Porter 1995). Other treatment-related stressors include the side effects of opioids, sedative and anxiolytic drugs, and drug-induced dizziness (Porter 1995).

Stressful environmental factors that are frequently reported include noise caused by beeping machines and the caregiving staff, ambient light, and social isolation (Rotondi et al.

The video of presentation is shown online:

2002, Chahraoui 2015). The World Health Organization (WHO) recommends that the noise in rooms where patients are being treated or observed should not exceed 35 decibels (dB) during the day and that peaks in noise during the night should not exceed 40 dB (Berglund 1999). These WHO recommendations are commonly exceeded in ICUs (Darbyshire and Young 2013). Artificial light that is continuously on throughout the day and night as well as limited exposure to natural light lead to the disturbance of circadian rhythms and corresponding sleep disruption, one of the most bothersome stressors in the ICU (Stewart et al. 2016, Weiss et al. 2016).

Critical illness and intensive care are an unexpected or sudden event for the majority of patients. Thus, a stay in the ICU is distressing for most patients. Patients interviewed about psychological stressors most frequently reported a fear of dying, uncertainly about the future and their healing prospects, lack of control and privacy, communication difficulties, helplessness, feelings of bewilderment, depersonalization, or loneliness (Rotondi et al. 2002, Granja et al. 2005). There are also emotional stressors, for example, submission to caregivers and family worries. Patients felt isolated from their families, friends, and the outside world, and reported feeling abandoned and having a lack of information (Chahraoui 2015). Missing one's spouse was a highly ranked psychological stressor in Soehren's survey of cardiac surgery patients (Soehren 1995). A study by Czerwonka et al. (2015) asked patients about their needs, and they described that information from health care professionals increases throughout different stages of recovery. Initially patients may be unable to process complex information about their state of health. Hence, it is very important that relatives receive information (Czerwonka et al. 2015).

In many interviews patients reported no initial memories of the ICU (Chahraoui 2015, Granja et al. 2005). A study by Ringdal (2006), which assessed memories of emergency room patients, revealed that 15 % of the participants had no memories of the ICU, and 83 % reported factual memories such as visits by family members (Ringdal et al. 2006). Fragmentary memories of the ICU often recur during interviews and follow-up investigations. About half of the patients described confusion about whether something was a dream or a reality, as well as temporal and spatial disorientation (Chahraoui 2015). Frightening nightmares and hallucinations were the most common recollections and associated with memories of pain, fear and panic (Ringdal et al. 2006). Since patients with delusional memories referred to unexplained feelings of panic after being discharged from the ICU, fearful dreams and nightmares also seem to affect them later in life (Granja et al. 2005, Ringdal et al. 2006).

However, patients also link the treatment of critical illness with positive experiences, mainly related to the support received from family and the health care team. Patients were aware of efforts by the nursing staff to provide them with mental and physical care. Many patients felt they were in good hands and were of the impression that they had been well cared for and supported (Chahraoui et al. 2015). Granja et al. (2005) analyzed patient recollections of experiences in the intensive care unit and, of the patients with memories, 93 % rated the ICU-environment as friendly and calm, and 73 % stated in the survey that they had had enough sleep (Granja et al. 2005). The majority of patients had the impression that their dignity was maintained and that they were treated with respect.

Patients and health care providers perceive and assess the needs and well-being of patients in the ICU very differently. This discrepancy became clear in a study by Schindler et al. (2013). The authors used questionnaires to examine the subjective ICU experience of patients as well the assumptions of staff members (physicians and nurses) about the patients' expe-

riences. The study identified so-called "client-professional gaps" which describe the gap between the experience of the patients during their ICU stay and the assumptions of the nursing staff regarding the patient experience in the ICU. These gaps affect communicative, intrapersonal and somatic dimensions. Whereas the majority (80 %) of patients claimed to be satisfied with ICU treatment, only 6.7 % of the nursing stuff assumed that the patients were satisfied. Furthermore, 74 % of patients felt they were able to communicate and be understood, but not one of the staff members felt this was the case. The discrepancy between patients and nurses in the assessment of ICU stressors was also evident when asked to rank stressors. For patients, "being in pain", "not being able to sleep" and "financial worries" were the top three stressors. In contrast, for the health care providers "being in pain", "not being able to communicate" and "not being in control of yourself" were the top three stressors mentioned. Moreover, health care professionals rated general stress levels higher than patients (Abuatiq 2015).

In our follow-up interviews it becomes clear that the well-being of many patients is impaired by mental stress while staying in the ICU as well as by the long-term consequences of the disease and the side effects of treatment. For example, delusional memories seem to impair psychological recovery. The symptoms of anxiety and posttraumatic stress disorder of patients after ICU discharge were significantly higher for patients reporting only delusional memories compared to patients with factual memories (Jones et al. 2001, Granja et al. 2008). In addition, nightmares and delusional memories during ICU stays have a negative impact on the health-related quality of life and "back-to-work rate" (Ringdal et al. 2006). 41 % of patients reported sleep disturbances, about one-third of patients had difficulties in concentrating during daily activities and in remembering recent events. More than half of the patients reported being more fatigued than before their ICU stay (Granja et al. 2005). Cognitive impairments, especially in conjunction with delirium, are often documented (Girard et al. 2010, Hopkins et al. 2005).

A stakeholders' meeting of non-critical care providers and survivors defined impairments after critical illness as "post-intensive care syndrome" – so called PICS – which describes acquiring new or worsening health problems after critical illness that persist after leaving the hospital. These problems may include physical issues, thoughts, feelings, or mental issues and may affect patients or their families (PICS-F) (Elliott et al. 2014, Needham et al. 2012). The sequelae may be long-lasting and affect the patient's quality of life.

Different strategies to support mental function during a critical illness and to prevent long-term impairments are discussed: the presence of family, cognitive stimulation, minimizing sedation, early mobilization, and physical contact. Since delusional memories have a significant impact on mental recovery, ICU diaries are provided by nurses to record the events of intensive care treatment. With the help of this diary, the patient may later be more able to understand what has happened, which could support mental recovery (Garrouste-Orgeas et al. 2012).

Both the perception of stress in the ICU as well as the long-term consequences of the critical diseases are influenced by a variety of factors. A patient's personality traits and social support play an important role in processing the critical illness and associated stressors. Patients who had family members accompanying them during their ICU stay reported lower stress levels (Abuatiq 2015). Psychological resilience factors, such as the development of coping strategies, access to social support, cognitive flexibility and mindfulness are important for the healing process. Early psychological support for critical illness might be a way to develop resilience in dealing with a critical situation.

References

Abuatiq, A.: Patients' and health care providers' perception of stressors in the intensive care units. Dimensions of Crit. Care Nursing (DCCN) *34*/4, 205–214 (2015)

Berglund, B.: LTaSDHe, Guidelines for Community Noise. Geneva: World Health Organization 1999

Chahraoui, K., Laurent, A., Bioy, A., and Quenot, J. P.: Psychological experience of patients 3 months after a stay in the intensive care unit. A descriptive and qualitative study. J. Crit. Care *30*/3, 599–605 (2015)

Czerwonka, A. I., Herridge, M. S., Chan, L., Chu, L. M., Matte, A., and Cameron, J. I.: Changing support needs of survivors of complex critical illness and their family caregivers across the care continuum, a qualitative pilot study of Towards RECOVER. J. Crit. Care *30*/2, 242–249 (2015)

Darbyshire, J. L., and Young, J. D.: An investigation of sound levels on intensive care units with reference to the WHO guidelines. Crit. C are (London, England) *17*/5, R187 (2013)

Elliott, D., Davidson, J. E., Harvey, M. A., Bemis-Dougherty, A., Hopkins, R. O., Iwashyna, T. J., Wagner, J., Weinert, C., Wunsch, H., Bienvenu, O. J., Black, G., Brady, S., Brodsky, M. B., Deutschman, C., Doepp, D., Flatley, C., Fosnight, S., Gittler, M., Gomez, B. T., Hyzy, R., Louis, D., Mandel, R., Maxwell, C., Muldoon, S. R., Perme, C. S., Reilly, C., Robinson, M. R., Rubin, E., Schmidt, D. M., Schuller, J., Scruth, E., Siegal, E., Spill, G. R., Sprenger, S., Straumanis, J. P., Sutton, P., Swoboda, S. M., Twaddle, M. L., and Needham, D. M.: Exploring the scope of post-intensive care syndrome therapy and care, engagement of non-critical care providers and survivors in a second stakeholders meeting. Crit. Care Med. *42*/12, 2518–2526 (2014)

Garrouste-Orgeas, M., Coquet, I., Perier, A., Timsit, J. F., Pochard, F., Lancrin, F., Philippart, F., Vesin, A., Bruel, C., Blel, Y., Angeli, S., Cousin, N., Carlet, J., and Misset, B.: Impact of an intensive care unit diary on psychological distress in patients and relatives. Crit. Care Med. *40*/7, 2033–2040 (2012)

Girard, T. D., Jackson, J. C., Pandharipande, P. P., Pun, B. T., Thompson, J. L., Shintani, A. K., Gordon, S. M., Canonico, A. E., Dittus, R. S., Bernard, G. R., and Ely, E. W.: Delirium as a predictor of long-term cognitive impairment in survivors of critical illness. Crit. Care Med. *38*/7, 1513–1520 (2010)

Granja, C., Gomes, E., Amaro, A., Ribeiro, O., Jones, C., Carneiro, A., and Costa-Pereira, A.: Understanding posttraumatic stress disorder-related symptoms after critical care, the early illness amnesia hypothesis. Crit. Care Med. *36*/10, 2801–2809 (2008)

Granja, C., Lopes, A., Moreira, S., Dias, C., Costa-Pereira, A., and Carneiro, A.: Patients' recollections of experiences in the intensive care unit may affect their quality of life. Crit. Care (London, England) *9*/2, R96–109 (2005)

Hopkins, R. O., Weaver, L. K., Collingridge, D., Parkinson, R. B., Chan, K. J., and Orme, J. F. Jr.: Two-year cognitive, emotional, and quality-of-life outcomes in acute respiratory distress syndrome. Amer. J. Respir Crit. Care Med. *171*/4, 340–347 (2005)

Jones, C., Griffiths, R. D., Humphris, G., and Skirrow, P. M.: Memory, delusions, and the development of acute posttraumatic stress disorder–related symptoms after intensive care. Crit. Care Med. *29*/3, 573–580 (2001)

Kalfon, P., Mimoz, O, Auquier, P., Loundou, A., Gauzit, R., Lepape, A., Laurens, J., Garrigues, B., Pottecher, T., and Malledant, Y.: Development and validation of a questionnaire for quantitative assessment of perceived discomforts in critically ill patients. Intensive Care Med. *36*/10, 1751–1758 (2010)

Needham, D. M., Davidson, J., Cohen, H., Hopkins, R. O., Weinert, C., Wunsch, H., Zawistowski, C., Bemis-Dougherty, A., Berney, S. C., Bienvenu, O. J., Brady, S. L., Brodsky, M. B., Denehy, L., Elliott, D., Flatley, C., Harabin, A. L., Jones, C., Louis, D., Meltzer, W., Muldoon, S. R., Palmer, J. B., Perme, C., Robinson, M., Schmidt, D. M., Scruth, E., Spill, G. R., Storey, C. P., Render, M., Votto, J., and Harvey, M. A.: Improving long-term outcomes after discharge from intensive care unit, report from a stakeholders' conference. Crit. Care Med. *40*/2, 502–509 (2012)

Porter, L. A.: Procedural distress in critical care settings. Crit. Care Nursing Clinics of North America *7*/2, 307–314 (1995)

Ringdal, M., Johansson, L., Lundberg, D., and Bergbom, I.: Delusional memories from the intensive care unit-experienced by patients with physical trauma. Intensive Crit. Care Nursing *22*/6, 346–354 (2006)

Rotondi, A. J., Chelluri, L., Sirio, C., Mendelsohn, A., Schulz, R., Belle, S., Im, K., Donahoe, M., and Pinsky, M. R.: Patients' recollections of stressful experiences while receiving prolonged mechanical ventilation in an intensive care unit. Crit. Care Med. *30*/4, 746–752 (2002)

Schindler, A. W., Schindler, N., Enz, F., Lueck, A., Olderog, T., and Vagts, D. A.: ICU personnel have inaccurate perceptions of their patients' experiences. Acta anaesthesiologica Scandinavica *57*/8, 1032–1040 (2013)

Soehren, P.: Stressors perceived by cardiac surgical patients in the intensive care unit. Amer. J. Crit. Care (Amer. Assoc. Critical-Care Nurses) *4*/1, 71–76 (1995)

Stewart, J. A., Green, C., Stewart, J., and Tiruvoipati, R.: Factors influencing quality of sleep among non-mechanically ventilated patients in the Intensive Care Unit. Aust. Crit. Care 2016

Weiss, B., Spies, C., Piazena, H., Penzel, T., Fietze, I., and Luetz, A.: Exposure to light and darkness and its influence on physiological measures of intensive care unit patients–a systematic literature review. Physiol. Meas. *37*/9, R73–87 (2016)

Dr. Claudia Denke
Department of Anaesthesiology and
Intensive Care Medicine,
Campus Charité Mitte
and Campus Virchow-Klinikum
Charité – Universitätsmedizin Berlin
13353 Berlin
Germany
Tel.: +49 30 450551138
Fax: +49 30 450551900
E-Mail: claudia.denke@charite.de

Intensive Care 2017:
A High Price for Everyone

Nova Acta Leopoldina NF Nr. *421*, 47–48 (2018)

After Struggling with Death: What Price Does the Patient Pay for Survival?

Nathan Brummel (Nashville, TN, USA)

Abstract

Up to 75 % of Intensive Care Unit (ICU) survivors suffer from long-term ICU-acquired disabilities that impair physical and cognitive function mainly as a result of deep sedation and bed rest. New strategies like reducing sedation and early mobilization are tackling these problems and will hopefully result in improved quality of life after ICU care.

Zusammenfassung

Bis zu 75 % der Überlebenden nach einem Aufenthalt auf der Intensivstation leiden unter langanhaltenden, auf der Intensivstation entstandenen Beeinträchtigungen, die physische und kognitive Funktionen vor allem wegen tiefer Sedierung und Bettruhe schwächen. Neue Strategien wie die reduzierte Sedierung und eine frühe Mobilisierung lösen diese Probleme und führen hoffentlich zu einer verbesserten Lebensqualität nach der Intensivpflege.

The ability to function independently is the most important factor in health care utilization and for health-related quality of life. The single greatest risk factor for loss of independence in activities of daily living (ADLs) is hospitalization, particularly for a critical illness. The annual number of people surviving critical illness has doubled in the last 20 years. Thus, critical illness survivorship is an emerging, under-addressed, and age-related public health issue. Each year 1.4 million older Americans, and many more worldwide, survive a critical illness. Up to 75 % suffer from long-term, newly acquired or deteriorating disabilities in ADLs and impairments in physical and cognitive function. Those with frailty, a syndrome present in one in three Intensive Care Unit (ICU) patients, are at the greatest risk. Survivors consume substantial health care resources while, at the same time, face a near-total loss of their life savings.

These survivors of critical illness with new or worsened disabilities and impairments are facing problems that prior generations did not face as the latter succumbed to their illness. We, as a critical care community, are only now beginning to understand the risk factors for these problems, now termed Post-ICU Syndrome (PICS). Until recently, deep sedation and bed rest were believed to be a necessary part of treating critical illness, until studies describing significant disabilities and physical and cognitive impairments in survivors of critical illness led us to reevaluate these practices. Conscious patients can safely and feasibly start to

The video of presentation is shown online:

participate in early mobility in the ICU, although data from randomized trials are conflicting and inconclusive with regard to the effect of activity on long-term disability and physical and cognitive function. Low levels of activity are associated with ADL disability in older adults who are hospitalized but not critically ill. The pathways by which low activity may lead to disability remain unclear. Delirium, particularly its hypoactive subtype, for example, is common in the ICU, and its duration predicts ADL disability and cognitive impairment.

To inform the discussion of the personal cost of surviving a critical illness, we will first describe the severity of disabilities and impairments suffered by survivors of critical illness. We will then review a conceptual model of the disabling process. Using data from recent clinical trials, we will build on that model to better understand the relationship between the potentially modifiable PICS risk factors of sedation, delirium and immobility. Finally, we will highlight important areas in need of future research related to the complex, multidimensional process of PICS in survivors of critical illness.

References

Brummel, N. E., Balas, M. C., Morandi, A., Ferrante, L. E., Gill, T. M., and Ely, E. W.: Understanding and reducing disability in older adults following critical illness. Crit. Care Med. *43*, 1265–1275 (2015)

Gill, T. M., Allore, H. G., Holford, T. R., and Guo, Z.: Hospitalization, restricted activity, and the development of disability among older persons. JAMA *292*, 2115–2124 (2004)

Herridge, M. S., Tansey, C. M., Matté, A., Tomlinson, G., Diaz-Granados, N., Cooper, A., Guest, C. B., Mazer, C. D., Mehta, S., Stewart, T. E., Kudlow, P., Cook, D., Slutsky, A. S., Cheung, A. M., and *Canadian Critical Care Trials Group*: Functional disability 5 years after acute respiratory distress syndrome. New Engl. J. Med. *364*, 1293–1304 (2011)

Jackson, J. C., Pandharipande, P. P., Girard, T. D., Brummel, N. E., Thompson, J. L., Hughes, C. G., Pun, B. T., Vasilevskis, E. E., Morandi, A., Shintani, A. K., Hopkins, R. O., Bernard, G. R., Dittus, R. S., Ely, E. W., and *Bringing to Light the Risk Factors and Incidence of Neuropsychological Dysfunction in ICU Survivors (BRAIN-ICU) Study Investigators*: Depression, post-traumatic stress disorder, and functional disability in survivors of critical illness in the BRAIN-ICU study: a longitudinal cohort study. Lancet Respir. Med. *2*, 369–379 (2014)

Needham, D. M., Davidson, J., Cohen, H., Hopkins, R. O., Weinert, C., Wunsch, H., Zawistowski, C., Bemis-Dougherty, A., Berney, S. C., Bienvenu, O. J., Brady, S. L., Brodsky, M. B., Denehy, L., Elliott, D., Flatley, C., Harabin, A. L., Jones, C., Louis, D., Meltzer, W., Muldoon, S. R., Palmer, J. B., Perme, C., Robinson, M., Schmidt, D. M., Scruth, E., Spill, G. R., Storey, C. P., Render, M., Votto, J., and Harvey, M.: Improving long-term outcomes after discharge from intensive care unit: Report from a stakeholders' conference. Crit. Care Med. *40*, 502–509 (2012)

Pandharipande, P. P., Girard, T. D., Jackson, J. C., Morandi, A., Thompson, J. L., Pun, B. T., Brummel, N. E., Hughes, C. G., Vasilevskis, E. E., Shintani, A. K., Moons, K. G., Geevarghese, S. K., Canonico, A., Hopkins, R. O., Bernard, G. R., Dittus, R. S., Ely, E. W., and *BRAIN-ICU Study Investigators*: Long-term cognitive impairment after critical illness. New Engl. J. Med. *369*, 1306–1316 (2013)

Nathan E. Brummel, M.D., M.S.C.I.
Assistant Professor of Medicine
Center for Quality Aging
Division of Allergy, Pulmonary, and Critical Care Medicine
Vanderbilt University Medical Center
2525 West End Ave., Suite 350
Nashville, TN 37203
USA
Tel.: +1 615 3433957
Fax: +1 615 3221754
E-Mail: nathan.brummel@vanderbilt.edu

Nova Acta Leopoldina NF Nr. *421*, 49–50 (2018)

What is PICS from a Public Health Point of View?

Hannah Wunsch (Toronto, ON, Canada)

Abstract

Post-Intensive Care Syndrome (PICS) comprises newly acquired cognitive deficits, mental illnesses, i.e. depression and anxiety, as well as physical problems that arise after surviving a critical illness. Currently we are unable to identify patients at a high risk for PICS who need special post-intensive care. This gap has major public health implications in terms of the cost of care and quality of life of Intensive Care Unit (ICU) survivors.

Zusammenfassung

Das *Post-Intensive Care Syndrome* (PICS) umfasst neu entstandene kognitive Defizite, psychische Erkrankungen, z. B. Depressionen und Angst, sowie körperliche Beschwerden nach dem Überstehen einer kritischen Erkrankung. Derzeit sind wir nicht in der Lage, Patienten mit einem hohen Risiko für PICS, die eine spezielle Behandlung nach einem Aufenthalt auf der Intensivstation benötigen, zu identifizieren. Diese Lücke hat schwerwiegende Folgen für das Gesundheitswesen hinsichtlich der Pflegekosten und der Lebensqualität von Überlebenden nach einem Aufenthalt auf der Intensivstation.

The concept of Post-Intensive Care Syndrome (PICS) has been evolving over the past 15 years as we collect more and more data on the extent of specific types of morbidity after critical illness. The term itself was coined by a taskforce sponsored by the Society of Critical Care Medicine in 2012. It focuses on the idea that there are common problems that may affect large groups of patients after exposure to intensive care (Needham et al. 2012). These concerns include cognitive deficits, mental illnesses, such as depression and anxiety, and physical problems.

An individual may have one or many of these problems following a critical illness, or none at all. It is important to differentiate between a new problem created by the critical illness or related treatments, and a problem that existed prior to hospitalization (Cuthbertson and Wunsch 2016). Cohort studies that merely measure symptoms and scores after hospital discharge, without referencing pre-hospital status, will overestimate the burden of PICS. Similarly, it is important to note that many of the problems identified in cohorts of patients after intensive care are also concerns for individuals who are hospitalized without critical illness.

The video of presentation is shown online:

Studies that are able to control for hospitalized patients who are not critically ill allow us to better understand the risk attributed to the critical illness and care received in the Intensive Care Unit (ICU).

As mortality from critical illnesses decreases, we have many more survivors (Iwashyna et al. 2012). However, the burden of PICS at the population level first has to be measured with the knowledge that mortality, both while the patient is hospitalized with the critical illness and afterwards, remains high for many diseases such as the Acute Respiratory Distress Syndrome (ARDS). Second, the challenge of understanding PICS from a public health perspective is to identify the true total burden of morbidity that is associated specifically with critical illness, and to determine the subgroups of patients who may be at high risk and who could benefit from close screening. Many studies identify a slight risk of developing new mental or physical disabilities. However, given the large volume of patients who pass through ICUs, these small increases in odds do not allow for high risk groups to be truly identified and may contribute to over-extension of resources in post-intensive care in an attempt to reach all or many relatively low-risk survivors (Cuthbertson et al 2009). Finally, we still lack information about what the implications are to public health in terms of cost of care and loss of earnings for survivors of critical illnesses resulting specifically from PICS.

References

Cuthbertson, B. H., and Wunsch, H.: Long-term outcomes after critical illness. The best predictor of the future is the past. Amer. J. Respir Crit. Care Med. *194*/2, 132–134 (2016)

Cuthbertson, B. H., Rattray, J., Campbell, M. K., Gager, M., Roughton, S., Smith, A., Hull, A., Breeman, S., Norrie, J., Jenkinson, D., Hernández, R., Johnston, M., Wilson, E., Waldmann, C., and *PRaCTICaL Study Group*: The PRaCTICaL study of nurse led, intensive care follow-up programmes for improving long term outcomes from critical illness: a pragmatic randomised controlled trial. BMJ *339*, b3723 (2009)

Iwashyna, T. J., Cooke, C. R., Wunsch, H., and Kahn, J. M.: Population burden of long-term survivorship after severe sepsis in older Americans. J. Amer. Geriatr. Soc. *60*/6, 1070–1077 (2012)

Needham, D. M., Davidson, J., Cohen, H., Hopkins, R. O., Weinert, C., Wunsch, H., Zawistowski, C., Bemis-Dougherty, A., Berney, S. C., Bienvenu, O. J., Brady, S. L., Brodsky, M. B., Denehy, L., Elliott, D., Flatley, C., Harabin, A. L., Jones, C., Louis, D., Meltzer, W., Muldoon, S. R., Palmer, J. B., Perme, C., Robinson, M., Schmidt, D. M., Scruth, E., Spill, G. R., Storey, C. P., Render, M., Votto, J., and Harvey, M. A.: Improving long-term outcomes after discharge from intensive care unit: Report from a stakeholders' conference. Crit. Care Med. *40*/2, 502–509 (2012)

Hannah Wunsch, MD MSc
Sunnybrook Health Sciences Centre
2075 Bayview Ave., Room D1 08a
Toronto, ON, M4N 3M5
Canada
Tel.: +1416 4806100, ext. 5022
Fax: +1416 4804999
E-Mail: hannah.wunsch@sunnybrook.ca

Nova Acta Leopoldina NF Nr. *421*, 51–52 (2018)

Regaining Strength after the ICU

Ursula Müller-Werdan (Berlin)

Abstract

The skeletal muscle has yet to be included in conventional medical analyses of the intensive care unit (ICU). Geriatric patients are particularly vulnerable to critical illness due to a gradual decline in physiological reserve of all organ functions and are therefore susceptible to multiple organ failure with a loss in cerebral or autonomic function and muscular strength. Regaining physical and mental strength after ICU care in the geriatric population is particularly challenging and prompts the need for new treatment strategies.

Zusammenfassung

Der Skelettmuskel ist bisher noch nicht hinreichend in den herkömmlichen medizinischen Auswertungen der Intensivstation abgebildet. Geriatrische Patienten sind besonders anfällig für kritische Erkrankungen aufgrund einer sukzessiven Abnahme der physiologischen Reserven aller Organfunktionen, und sie sind somit gefährdet für Multiorganversagen mit einem Verlust der zerebralen und autonomen Funktion und Muskelstärke. Die Wiedererlangung körperlicher und mentaler Stärke bei der betagten Bevölkerung nach der Intensivpflege stellt eine besondere Herausforderung dar und zeigt das Erfordernis neuer Behandlungsstrategien.

While highly standardized diagnostic tools are used to scrupulously monitor the parenchymal organs (kidney, liver and cardiac function) of critically ill patients, skeletal muscle mass and function are often only observed qualitatively. There is no gold standard for examining the fascial compartment of the body, and skeletal muscle is not a focus of our conventional medical analysis despite the fact that muscle mass and strength have been shown to be major determinants of both prognosis and recovery from severe disease. The medical team providing care to a critically ill patient will most certainly be interested in his or her cognitive functions so as not to overlook delirium, yet the function of the autonomic nervous system is often not afforded the same care and attention. Recent studies indicate that, in all age groups, autonomic dysfunction is a major prognostic factor in Intensive Care Unit (ICU) patients and may prompt multiple organ failure.

Geriatric patients are particularly susceptible to multiple organ failure, even in the absence of overt organ disease. This is caused by a gradual decline in physiological reserve ("homoeostenosis" according to Resnick and Marcantonio 1997) of all organ functions. Due to compromised homoeostatic mechanisms, disease often presents at an earlier stage than in

The video of presentation is shown online:

younger individuals, and recovery from critical illness may be prolonged. The most vulnerable organ system ("weakest link") is supposed to provoke the dominant clinical presentation in geriatric patients. The "weakest link" in many cases may be cerebral function, muscular strength or autonomic function, which, in any event, decline in the course of the physiological aging process and give rise to a heightened vulnerability in the geriatric population when challenged with a life-threatening disease.

Regaining physical and mental strength after a stay in the ICU requires that the fascial compartment, the autonomic nervous system and cerebral functions be monitored so as to form a basis for complex interventions by the multidisciplinary treatment team.

References

Heppner, H. J., Sieber, C., und Singler, K.: Intensivmedizin im Alter. Dtsch. Med. Wochenschr. *138*, 176–179 (2013)

Leblanc, G., Boumendil, A., and Guidet, B.: Ten things to know about critically ill elderly patients. Intensive Care Med. *43*/2, 217–219, doi:10.1007/s00134-016-4477-2 (2017)

Meisel, M., Nuding, S., und Müller-Werdan, U.: Assessment des älteren Intensivpatienten [Assessment of elderly intensive care patients]. Med. Klin. Intensivmed. Notfmed. *107*, 29–31 (2012)

Müller-Werdan, U., Klöss, T., und Meisel, M.: Medizinisch-geriatrische Aspekte in der Intensivtherapie alter Patienten [Medical geriatric aspects in intensive care therapy of elderly patients]. Med. Klin. Intensivmed. *106*, 10–15 (2011)

Resnick, N. M., and Marcantonio, E. R.: How should clinical care of the aged differ? Lancet *350*, 1157–1158 (1997)

Schmidt, H., Hoyer, D., Hennen, R., Heinroth, K., Rauchhaus, M., Prondzinsky, R., Hottenrott, K., Buerke, M., Müller-Werdan, U., and Werdan, K.: Autonomic dysfunction predicts both 1- and 2-month mortality in middle-aged patients with multiple organ dysfunction syndrome. Crit. Care Med. *36*, 967–970 (2008)

Schmidt, H., Lotze, U., Ghanem, A., Anker, S. D., Said, S. M., Braun-Dullaeus, R., Oltmanns, G., Rose, S., Buerke, M., Müller-Werdan, U., Werdan, K., and Rauchhaus, M.: Relation of impaired interorgan communication and parasympathetic activity in chronic heart failure and multiple-organ dysfunction syndrome. J. Crit. Care *29*, 367–373 (2014)

Prof. Dr. Ursula Müller-Werdan
Charité – Universitätsmedizin Berlin
Department of Geriatrics
and Protestant Geriatric Centre Berlin
Reinickendorfer Straße 61
13347 Berlin
Bundesrepublik Deutschland
Tel.: +49 30 45941901
Fax: +49 30 45941938
E-Mail: ursula.mueller-werdan@charite.de

Nova Acta Leopoldina NF Nr. *421*, 53–57 (2018)

Multisystem Organ Failure: Why Doctors Look at the Wrong Organs

Hans Flaatten (Bergen, Norway)

Abstract

During multiple organ failure, traditional organ dysfunction is of primary importance and needs to be identified and treated. Some other organs, however, are just as relevant but are often not considered during critical illness until it is too late: the gastrointestinal (GI) tract, neuro-muscular system and central nervous system (CNS) function. Early recognition of failure in these organs and prevention are of prime importance at a time of patient-centered outcomes.

Zusammenfassung

Bei vielfachem Organversagen ist die ursprüngliche Organdysfunktion von primärer Bedeutung und muss erkannt und behandelt werden. Einige weitere Organe sind jedoch genauso wichtig, werden bei kritischen Krankheiten aber oft zu spät berücksichtigt: der Magendarmtrakt, das neuromuskuläre System und die Funktion des zentralen Nervensystems. Ein frühzeitiges Erkennen von Störungen in diesen Organen und entsprechende Prävention sind in einer Zeit von patientenorientierter Folgenbewertung von vorrangiger Bedeutung.

1. Introduction

Multisystem organ failure (MOF) has been closely connected with intensive care for at least 50 years. Probably the first systematic report on the issue emerged in the *Annals of Surgery* in 1973, which documented 18 patients treated in the Intensive Care Unit (ICU) after a ruptured aortic aneurism (Tilney et al. 1973). These patients developed what was then called sequential system failure and only one patient survived. Since that time the clinical picture has been given several names: most often it is called multi-system organ failure or dysfunction, and the pathophysiology behind the picture has changed from mere descriptions of connections to a deeper understanding of mechanisms (Mongardon et al. 2009). Still, this syndrome is far from understood and even seems to change over time.

It is interesting to note how the list of the major organs involved in failure or dysfunction has changed since its original publication (Tab. 1), with the abdominal organs, apart from the liver, having disappeared from the list.

The video of presentation is shown online:

Today this is mirrored in the most frequently used organ dysfunction scores: Sequential Organ Failure Assessment (SOFA), Multiple Organ Dysfunction Score (MODS) and Logistic Organ Dysfunction Score (LODS) (Vincent et al. 1996, Strand and Flaatten 2008), which are all based on only six organs.

Tab. 1 Understanding multi-organ failure over time

	Tilney et al. 1973	Deitch 1992	Vincent et al. 1996
Pancreas	yes	no	no
Lungs	yes	yes	yes
Kidney	yes	yes	yes
Liver	yes	yes	yes
CNS	yes	yes	yes
Heart	yes	yes	yes
Coagulation	no	yes	yes
Lower GI	yes	yes, intestinal	no
Upper GI	yes		no

This universal consensus on MOF is probably a major reason why we as ICU physicians have focused for a long time on these "vital organ systems", although there are others that are probably just as important when it comes to the initiation of MOF or to the important consequences for survivors after critical care.

2. What initiates MOF?

This has been a puzzle since the concept was first conceived and is still far from completely understood. The "gut hypothesis", first raised by Meakin and Marshal in 1985 (Carrico et al. 1986), has been discussed for a long time. Although not proven, the gut undoubtedly is a Damocles sword in critical illness. The volume of bacteria and endotoxins is enormous, and translocation of such content across the gut barrier may have far-reaching consequences for the rest of the body. Although the gut is often a silent organ in critical illness (literally speaking) this does not imply it is a healthy organ – on the contrary. For a long time we have let the gut "rest in peace" during critical illness and have often not started enteral feeding until many days into the critical care period. The trend of early enteral nutrition, also in the most critically ill patients, seems to have favorable effects, and has been found to be superior to parenteral or no nutrition in some groups (trauma, burns, pancreatitis) (*ESPEN* 2013).

Although not widely recognized, selective digestive decontamination has been found to decrease mortality in ICU patients, with fewer infectious complications (Silvestri and Saene 2012). A reduction in traditional acute organ dysfunction has also been demonstrated with this treatment strategy (Silvestri et al. 2010). Both studies are powerful indications that the gut flora may play a significant negative role outside the gastro-intestinal system.

This highlights the importance of a functioning GI tract from the early onset of critical illness, and it should be reintroduced to the list of major failing organs (Sertaridou et al. 2015).

3. Another "Silent" Form of Organ Dysfunction

Disturbed neuro-muscular function is seldom considered in the context of MOF. ICU-acquired weakness may affect 25 to 65 % of patients on mechanical ventilation (Hermans and van den Berghe 2015) and is associated with increased hospital lengths of stay (LOS), increased length of mechanical ventilation and a higher rate of mortality. Maybe the most feared consequence is the long-term, sometimes lifelong, impairment of neuromuscular function (see case description).

Case description:
During the pandemic flu of 2009–2010, our ICU received a young patient who rapidly developed severe multi-organ failure necessitating prolonged mechanical ventilation including a period with high frequency oscillation. She had severe cardiovascular failure plus an episode of cardiac arrest, further acute renal failure, hepatic dysfunction, coma and bleeding. This was the first patient in our ICU to ever have a SOFA score of 24 and survive critical illness since we started using this as a daily score in 1999. As organ dysfunctions recovered, we gradually became aware of severe neuro-muscular dysfunction in our patient, with clinical evidence of a complete tetraplegia but preserved sensory function. Critical illness polyneuro-myopathy was confirmed through electromyography (EMG) and nerve conductance tests. Seven years later this patient is still dependent on a wheelchair and lives in a sheltered home.

Such organ dysfunction may be preventable – at least in part – by avoiding known risk factors, particularly prolonged immobilization and hyperglycemia and possibly also neuromuscular blockers and steroids (Hermans and van den Berghe 2015). Hence early mobilization and physical rehabilitation seems to help. Studies have demonstrated that even mobilizing ventilated patients 24 – 48 hours after intubation is feasible (Truong et al. 2009). A small controlled study has also found that early intervention results in better outcomes at hospital discharge, including a return to independent function, physical activity and more ventilator-free days (Schweickert et al. 2009). Interestingly, this intervention also led to a lower rate of delirium in the intervention group. It goes without saying that this will be very difficult with the "traditional" heavy sedation that mechanically ventilated, critically ill patients very often receive and adds to the iatrogenic injury such therapy may inflict on our patients.

4. CNS Dysfunction under the "Radar"

Although CNS dysfunction/failure has been on the list since MOF was first described, the current method of registering/scoring CNS problems in ICU patients is insufficient. Of the three systems used to score organ dysfunction, the Glasgow Coma Scale (GCS) is used to describe increasing failure. However, GCS was originally developed to describe unconsciousness in patients with traumatic brain injury (Teasdale and Jennett 1974) but has since been used and misused in clinical settings never originally conceived of.

Coma is of course not uncommon in ICU patients, but today we more often experience other signs of brain dysfunction in our patients such as:

– agitation,
– delirium,
– cognitive dysfunction,
– severe depression,
– cerebral drug effects,
– seizures.

None of these disorders are particularly well described using GCS, and hence are not picked up using our usual organ failure scores. This is not unexpected; to squeeze CNS function into a scale from 15 to 3 is a huge oversimplification of the most complex organ in the body. Hence the item scored should probably only be termed coma, and not CNS dysfunction as such.

However, the long list of CNS dysfunction observed in our ICU patients is important, but seldom well described. One year in our ICU we counted fewer than 10 patients with ICD-10 codes for delirium, although this is as common in our ICU as elsewhere! With the growing number of very old patients in the ICU this type of organ dysfunction will most likely increase, since advanced age is one of the major risk factors for this complication (Zaal et al. 2015). The incidence of this CNS dysfunction alone merits the use of daily delirium screening tests by all ICUs to pick up this diagnosis. Even if causal treatment is not possible at present, it is partially possible to prevent delirium using non-pharmacologic agents.

5. Conclusions

It would be impertinent to claim that the traditional organ dysfunctions and failures are unimportant; they must be identified and prevented and/or treated even though they will still inflict mortality and morbidity on our ICU patients. However, the awareness of these types of organ failure is high and we have come a long way in identifying, supporting and treating these organs until they, fortunately, often recover spontaneously. There are reasons to be more concerned about the more "silent" type of organ dysfunction that frequently passes unnoticed for a long time. We know enough about this additional burden to start a systematic search for it, to do our best to prevent it, and invest more resources to find effective cures.

References

Carrico, C. J., Meakins, J. L., Marshall, J. C., Fry, D., and Maier, R. V.: Multiple-organ-failure syndrome. Arch. Surg. *121*, 196–208 (1986)

Deitch, E. A.: Multiple organ failure. Ann Surg. *216*, 117–134 (1992)

ESPEN (The European Society for Clinical Nutrition and Metabolism): ESPEN endorsed recommendations: nutritional therapy in major burns. ESPEN Recommendations *32*/4, 497–502 (2013)

Hermans, G., and van den Berghe, G.: Clinical review: intensive care unit acquired weakness. Crit. Care *19*, 274 (2015)

Mongardon, N., Dyson, A., and Singer, M.: Is MOF an outcome parameter or a transient, adaptive state in critical illness. Curr. Opin. Crit. Care *15*, 431–436 (2009)

Schweickert, W. D., Pohlman, M. C., Pohlman, A. S., Nigos, C., Pawlik, A. J., Esbrook, C. L., Spears, L., Miller, M., Franczyk, M., Deprizio, D., Schmidt, G. A., Bowman, A., Barr, R., McCallister, K. E., Hall, J. B., and Kress, J. P.: Early physical and occupational therapy in mechanically ventilated, critically ill patients: a randomised controlled trial. Lancet. *373*/9678, 1874–1882 (2009)

Sertaridou, E., Papaioannou, V., Kolios, G., and Pneumatikos, I.: Gut failure in critical care: old school versus new school. Ann. Gastroent. *28*, 309–322 (2015)

Silvestri, L., and Saene, H. K. F.: Selective decontamination of the digestive tract: an update of the evidence. Proc. Int. Care Cardiovasc. Anaesth. *4*, 21–29 (2012)

Silvestri, L., Saene, H. K. F., Zandstra, D. F., Marshall, J. C., Gregori, D., and Gullo, A.: Impact of selective decontamination of the digestive tract on mutlitple organ dysfunction syndrome: Systematic review of randomized controlled trials. Crit. Care Med. *38*, 1370–1376 (2010)

Strand, K., and Flaatten, H.: Severity scoring in the ICU: a review. Acta Anaesthesiol. Scand. *52*, 467–478 (2008)

Teasdale, G., and Jennett, B.: Assessment of coma and impaired consciousness. Lancet *7872*, 81–84 (1974)
Tilney, N. L., Bailey, G. L., and Morgan, A. P.: Sequential organ failure after rupture of abdominal aortic aneurisms. Ann. Surg. *178*, 117–122 (1973)
Truong, A. D., Fan, E., Brower, R. G., and Needham, D. M.: Bench to bedside review: Mobilizing patients in the ICU-from pathophysiology to clinical trials. Crit. Care *13*, 216 (2009)
Vincent, J. L., Moreno, R., Takala, J., Willatts, S., Mendonça, A. de, Bruining, H., Reinhart, C. K., Suter, P. M., and Thijs, L. G.: The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. On behalf of the Working Group on Sepsis-Related Problems of the European Society of Intensive Care Med. *22*, 707–710 (1996)
Zaal, I. J., Devlin, J. W., Peelen, L. M., and Slooter, A. J. C.: A systematic review of risk factors for delirium in the ICU. Crit. Care Med. *43*/1, 40–47 (2015)

Prof. Hans Flaatten, MD PhD
Department of Anaesthesia and Intensive Care
Haukeland University Hospital
5021 Bergen
Norway
E-Mail: hans.flaatten@helse-bergen.no

Innovations and Basic Conditions

Nova Acta Leopoldina NF Nr. *421*, 61–64 (2018)

What's the Personal Price for Innovation? Looking Back on 10 Years of Enforcing and Managing a New ICU Concept

Jozef Kesecioglu (Utrecht, The Netherlands)

Abstract

New arrangements of the Intensive Care Units (ICU) with the best possible environment for critically ill patients and their relatives, i.e. innovative concepts like daylight, privacy and safety to provide patient-centered care, are a big challenge but advantages for each patient are evident. There is an obvious need to successive rebuilding our ICUs to improve patient-centered outcome.

Zusammenfassung

Neue Einrichtungen von Intensivstationen mit der bestmöglichen Umgebung für schwerkranke Patienten und deren Angehörige, d. h. innovative Konzepte wie Tageslichteinsatz, Privatsphäre und Vorsichtsmaßregeln für eine patientenorientierte Pflege, sind eine große Herausforderung, aber die Vorteile für jeden Patienten liegen auf der Hand. Es gibt eine unübersehbare Notwendigkeit, unsere Intensivstationen schrittweise zu erneuern, um die patientenorientierten Behandlungsresultate zu verbessern.

The University Medical Center Utrecht (UMC Utrecht) is a 1,040 bed hospital, which admits approximately 30,000 inpatients per year. All academic specialties are present, and the hospital provides a core service in heart and lung transplantations, ventricular assist devices, extracorporeal life support systems (ECLS), trauma, neurosurgery, oncology, hematology and AIDS patients.

In 2004, an independent survey measuring the quality of care and effectiveness of Intensive Care Units (ICUs) in the Netherlands concluded that UMC Utrecht performed adequately in this field, a stature which the hospital board subsequently felt could be improved. The first change to be made was in the overall structure of the ICU. Originally, the ICU was divided into four separate sectors: internal, surgical, cardio surgical and neurological/neurosurgical units, all of which were located in different parts of the hospital. In the new arrangement, these divisions were re-organized as a multidisciplinary medical department, marking the birth of a revolutionary project.

The video of presentation is shown online:

The organization of the multidisciplinary department was a big challenge (Bazuin and Cardon 2011). So far, physicians and nurses were used to work within their cluster. Insecurity, uncertainty on having the competence and fear were the main components.

Education and training, standardization of workflow, procedures, materials and equipment were the next steps. Standards of care for nurses and physicians were established. Surely, there were many moments of disagreement in the team. The question "What do the patient/family need?" has put the team back to the right track. Looking back the last 10 years, the achievements in several issues can be observed. An innovative workflow was created aimed completely on the needs of the patients and their family. Having one multidisciplinary department resulted in efficient use of beds. Each bed is available for any patient independent of the initial diagnosis, creating flexibility. A great change of culture in the physician and nurse teams have occurred. Next to identifying the problems only, presenting solutions as well has become standard.

The vision generated by this team was to create an intensive care department that produces the best possible environment for critically ill patients and their relatives, allowing doctors and nursing staff to focus on the patient. Patient-centered care, safety, functionality, innovation and future-proof concepts evolved as the main aspects of the new ICU design. Former patients and their family members were interviewed to assess opinions on the present condition of the department, including its shortcomings, and significant issues to be considered when building the new ICU were identified. Daylight, tranquil surroundings, patient privacy, adequate space, family comfort, ergonomics, logistics and safety were communicated as important, and concepts for improvements in these areas were developed.

In designing patient rooms, the well-being and orientation of the patient were considered of main concern; therefore, a key focus was the formation of a day and night rhythm. Each of the 36 single-patient rooms have a view either to either one of the four specially designed gardens or to other well lit spaces, providing sufficient daylight to the department.

The rooms are designed to make patients feel at home, featuring comfortable armchairs and fashionable lamps, among other attributes, all coordinated with soft warm colors. A clear glass wall and doors separates the room from the nursing staff, replacing what were old-fashioned curtains. The glass doors close automatically, unless kept deliberately open, providing a quiet environment for the patient. Furthermore, since the glass is electrostatic, meaning it instantly becomes opaque at the touch of a button, privacy is guaranteed whenever required.

The ceiling of each room is painted in soft blue with as few irregularities as possible, increasing the relaxing tone of patients' surroundings in the hope of lessening feelings of disorientation by patients suffering from delirium, a frequent occurrence in ICUs. Such patients commonly imagine strange phenomena emerging from the ceiling whereas in fact it may simply be an air conditioning duct. Simple aspects such as this are often overseen but can make a significant difference in patient comfort levels.

The benefits that could be generated for visiting relatives were not overlooked when forming the new ICU scheme, including from the perspective of the positive effects they have on the patient, as well as from the recognition that comfort and peace of mind have a significant effect on the overall atmosphere. A large area with catering and Internet facilities is reserved for family use, while a 24-hour visiting policy is applied, with no restrictions on visiting time.

With family values in mind, six double bedrooms, each with a bathroom and shower, were built in the unit for those relatives who live far away, or for specific cases where the patient is particularly ill. From the provision of PCs with Internet connection, cable TV and telephones, to outside meeting space and their own cafeteria, relatives are made to feel as welcome and as comfortable as possible. The family area is situated in a quiet corner of the floor so that members are not exposed to the daily activities of the intensive care department, giving them an atmosphere of privacy, security and trust.

It has been suggested that environmental improvements in ICU may affect family satisfaction (Zborowsky and Hellmich 2011). On the other hand, the effect of ICU environment on patient satisfaction has been suggested, based on studies in performed general wards (Trochelman et al. 2012, Kesecioglu et al. 2012). Recently, we have reported the results of a study performed in our ICU, with a before-after design, on the effect of ICU environment on both family and patient satisfaction (Jongerden et al. 2013). We have quantified the effect of ICU environment on both family and patient satisfaction, within a migrating ICU including a change in workflow, but with unaltered nurse–patient ratios, physician staffing and protocols. We demonstrated that family and patient satisfaction with ICU experience increased by 6 %, respectively, in the new ICU environment consisting of noise-reduced, single rooms with daylight, adapted coloring and improved family facilities.

In another study performed in the same ICU setting, we investigated the influence of ICU environment on the number of days with delirium during ICU admission (Zaal et al. 2012). The environment did not affect the incidence of delirium. However, our study showed that environmental factors reduced the number of days with delirium during ICU admission, broadening the evidence for the effectiveness of non-pharmacological measures in the treatment of delirium.

Before buying any required medical equipment, concepts were developed concerning functionality, safety and innovation. With these concepts subsequent choices on medical apparatus were made. The main themes considered when making decisions were the availability of a physician and nurse at the patient's bedside or nearby throughout their stay, ergonomics, safety and silence.

Each nurse carries a beeper, who receives specified patient alarms; the device can also be used to call for help in emergency situations. Medications and supplies are prepared and delivered to patients by the pharmacy personnel and logistics department, with most medicines prepared and delivered ready to use in syringes. The pharmacy located within the ICU prepares more than 80 % of the medicines used by its patients, reducing errors significantly.

The new intensive care department, especially the patients' rooms, has carefully been provided with a quiet and peaceful atmosphere. This has been achieved with new unit and concept design, spreading the medical and nursing personnel evenly across the floor instead of gathering them at the central post, and keeping the doors of the rooms mostly closed.

Looking back to the success of our concepts, we can conclude that an organization structured around the needs of the patient and family is mandatory in designing an effective intensive care department. Materials, apparatus and buildings eventually get old, but the concepts such as daylight, privacy and safety will always be the future. Concepts should, however, be developed and used also in choosing medical equipment so that the entire scheme developed will survive the test of time.

References

Bazuin, D., and Cardon, K.: Creating healing intensive care unit environments: physical and psychological considerations in designing critical care areas. Crit. Care Nurs. Q *34*, 259–267 (2011)

Jongerden, I. P., Slooter, A. J., Peelen, L. M., Wessels, H., Ram, C. M., Kesecioglu, J., Schneider, M. M., and van Dijk, D.: Effect of intensive care environment on family and patient satisfaction: a before-after study. Intensive Care Med. *39*, 1626–1634 (2013)

Kesecioglu, J., Schneider, M. M., van der Kooi, A. W., and Bion, J.: Structure and function: planning a new ICU to optimize patient care. Curr. Opin. Crit. Care *18*, 688–692 (2012)

Trochelman, K., Albert, N., Spence, J., Murray, T., and Slifcak, E.: Patients and their families weigh in on evidence-based hospital design. Crit. Care Nurse *32*/1, e1–e10 (2012)

Zaal, I. J., Spruyt, C. F., Peelen, L. M., van Eijk, M. M., Wientjes, R., Schneider, M. M., Kesecioglu, J., and Slooter, A. J.: Intensive care unit environment may affect the course of delirium. Intensive Care Med. *39*, 481–488 (2012)

Zborowsky, T., and Hellmich, L. B.: Impact of place on people and process: The integration of research on the built environment in the planning and design of critical care areas. Crit. Care Nurs. Q. *34*/1, 268–281 (2011)

Prof. Jozef Kesecioglu, MD, PhD
Chair
Division of Anesthesiology, Intensive Care
and Emergency Medicine
University Medical Center Utrecht
Heidelberglaan 100
3584 CX Utrecht
The Netherlands
Tel.: +31 88 7555555
E-Mail: jkesecio@umcutrecht.nl

Nova Acta Leopoldina NF Nr. *421*, 65–67 (2018)

An Economic Analysis of Intensive Care and the Time After Survival: It May Not Be Cost-Effective to Save at the Wrong End

Reinhard Busse (Berlin)

Abstract

Intensive care is expensive but can also be highly cost-effective. Still, there is a major gap between cost-effective intensive care and patient-centered intensive care that focuses on ideal patient-centered outcomes. This is something we have to address in our political and scientific decisions.

Zusammenfassung

Intensivpflege ist teuer, kann aber sehr kosteneffizient sein. Dennoch gibt es eine erhebliche Lücke zwischen kosteneffizienter Intensivpflege und patientenorientierter Intensivpflege, die den Fokus auf vorbildliche patientenorientierte Erfolge richtet. Dies ist etwas, womit wir uns in unseren politischen und wissenschaftlichen Entscheidungen befassen müssen.

Modern medicine is faced with several challenges: While the population is getting healthier, and thus older, the "need" for health care is not diminishing. Instead, new diagnostic and therapeutic procedures are being developed and offered to an increasing number of people (in part, precisely because they are healthier than previous generations). This poses questions concerning their effectiveness and appropriateness since the procedures are usually more expensive than the health care they replace or, more often, supplement. Evidence-based medicine, guidelines, and economic evaluations are tools that help address these challenges. The basic idea behind economic evaluations is simple and intriguing: they analyze whether additional ("incremental" in economic terms) costs represent good "value" for the – hopefully – additional benefits over the old (i.e standard) intervention (rather than looking solely at costs). Even in "normal" areas of health care, things become more complex when such evaluations are actually undertaken, for example with respect to cost: Which costs should we take into account – only those of the health care system, or also those of the patients and the society at large? How do we measure "costs" in the absence of market prices in major areas of health care? Methodological challenges are also expected with regard to effects: Which unit do we

The video of presentation is shown online:

use to measure effects? Changes in clinical values (blood pressure, heart rhythm …) even if they are possibly meaningless to the patient? Survival? Quality of life? Or a combination, usually termed "quality-adjusted life years" (QALYs)?

These challenges are even greater in intensive care, which is also why analyses are relatively rare, and the only systematic review is ten years old (Talmor et al. 2006). Applying the PICO (patients /population – intervention – control – outcomes) scheme to these challenges results in the following: (*1*) P – How do we define the patient group that potentially benefits from intensive care? Clearly it cannot simply be the patients admitted to intensive care in our units under observation. Instead we have to define them more specifically, e.g. as cases of severe sepsis, cardiac arrest or acute respiratory failure, and/or a score (e.g. APACHE) above a certain threshold. (*2*) I – What is the actual "intervention" when referring to intensive care? Intensive care is a "complex intervention", i.e. consisting of a variety of interventions, many of which could also be provided outside of an Intensive Care Unit (ICU; e.g. ventilation). While many studies on cost-effectiveness base intervention on individual interventions, the core definition should best be based on the availability of both personnel and certain technologies. (*3*) C – Who is the control group? In conventional economic evaluations, this is "usual care", "best available care" and/or "least costly care", but of course not using the intervention of interest, e.g. for patients with an acute respiratory failure, this would mean withholding ventilation. (*4*) O – What should be the outcome of interest? Survival in the short-term, mortality after one year or more? Ideally the necessity of continuous therapy and/or quality of life of the patient should be taken into account, i.e. a patient still requiring ventilation at home would count "less", thus making the intervention less cost-effective (e.g. in a US study on the cost-effects of mechanical ventilation, the results were $37,600 per life year saved but $174,200 per QALY [Mayer et al. 2000]).

However, the cost-effectiveness of intensive care not only depends on whether quality of life is taken into account but also on the P, the I, and the C. For example, more severely ill patients require more resources but also have (in spite of intensive care treatment) a higher mortality rate, i.e. the numerator of the cost-effectiveness ratio is higher than in less severely ill patients while the denominator also decreases. For example, in a Canadian study this led to a thirty-fold difference between patients admitted to ICU with severe sepsis and an APACHE score of up to 24 vs. 25 and more ($958,423 vs. $32,872 per QALY [Hamel et al 2001]). Other studies with a different definition of P, I and O have shown that intensive care treatment can be highly cost-effective (for example, an Australian study with a three-year follow-up revealed cost-effectiveness ratios of under $1,000 to around $3,000 per QALY for different patient groups [Kerridge et al. 1995]).

In summary, intensive care is expensive (in Germany around 13.5 % of hospital costs go towards intensive care treatment even though fewer than 6 % of patient days occur there, i.e. an average day in the ICU costs 2.5 times more than a non-ICU day [Bock et al. 2015]). The latest data from Canada shows a 3-fold difference (*Canadian Institute for Health Information* 2016), but – depending on the types of patients treated, the set of interventions applied, the alternative (given to the control group) and the chosen outcomes – it has also demonstrated that it can be cost-effective, i.e. "worth its money". Further research should examine the importance of these factors more explicitly to help intensive care concentrate on cost-effective patients and to make intensive care more cost effective for those treated in ICUs.

References

Bock, J.-O., Brettschneider, C., Seidl, H., Bowles, D., Holle, R., Greiner, W., und Koenig, H.-H.: Ermittlung standardisierter Bewertungssätze aus gesellschaftlicher Perspektive für die gesundheitsökonomische Evaluation. Das Gesundheitswesen *77*/1, 53–61 (2015)

Canadian Institute for Health Information: Care in Canadian ICUs. Ottawa: CIHI 2016

Hamel, M. B., Phillips, R. S., Davis, R. B., Teno, J., Desbiens, N., Lynn, J., and Tsevat, J.: Are aggressive treatment strategies less cost-effective for older patients? The case of ventilator support and aggressive care for patients with acute respiratory failure. J. Amer. Geriatr. Soc. *49*/4, 382–390 (2001)

Kerridge, R. K., Glasziou, P. P., and Hillman, K. M.: The use of "quality-adjusted life years" (QALYs) to evaluate treatment in intensive care. Anaesth. Intensive Care *23*/3, 322–331 (1995)

Mayer, S. A., Copeland, D., Bernardini, G. L., Boden-Albala, B., Lennihan, L., Kossoff, S., and Sacco, R. L.: Cost and outcome of mechanical ventilation for life-threatening stroke. Stroke *31*/10, 2346–2353 (2000)

Talmor, D., Shapiro, N., Greenberg, D., Stone, P. W., and Neumann, P. J.: When is critical care medicine cost-effective? A systematic review of the cost-effectiveness literature. Crit. Care Med. *34*/11, 2738–2747 (2006)

Prof. Dr. Reinhard Busse, MPH FFPH
Fakultät Wirtschaft und Management
Fachgebiet Management im Gesundheitswesen
Technische Universität Berlin
Straße des 17. Juni 135
10623 Berlin
Germany
Tel.: +49 30 31428420
Fax: +49 30 31428433
E-Mail: mig@tu-berlin.de

Nova Acta Leopoldina NF Nr. *421*, 69–73 (2018)

Designing a Healing Environment: What's Personal and Public Investment

Thomas Willemeit (Berlin)

Abstract

The architecture of the Intensive Care Unit (ICU), which includes a less stressful environment, i.e. a familiar, soothing physical environment within a natural circadian cycle, greatly impacts a patient's healing process and outcome. In most care facilities, the importance of a less stressful environment is underestimated. Collaboration with industry and the support of all stakeholders are necessary to continue and expand these important projects on patient-centered outcomes.

Zusammenfassung

Die Bauweise der Intensivstation, die eine weniger stressvolle Umgebung vorsieht, z. B. eine vertraute, beruhigende physikalische Umgebung innerhalb eines natürlichen Tagesrhythmus, wirkt sich in hohem Maße auf den Heilungsprozess und Behandlungserfolg eines Patienten aus. In den meisten Pflegeeinrichtungen wird die Bedeutung einer weniger stressvollen Umgebung verkannt. Die Zusammenarbeit mit der Industrie und die Unterstützung aller Interessenvertreter ist notwendig, um diese wichtigen Projekte für die patientenorientierten Behandlungserfolge fortzusetzen und auszubauen.

1. From Hospital to Hospitality: Architecture and Design of ICUs

The architecture of hospitals has long been considered to be primarily an exercise in functional discipline and hygiene. Only recently has the perception of architecture and its influence on the healing process started to be viewed as a factor in patient outcomes as well. Due to the complex nature of the relationship between atmospheric and medical "treatment", the number of research projects on the matter is limited. Such research requires a close collaboration between numerous experts and consultants on treatment and care, sleep and dream experts and architectural, acoustical and mechanical engineers. Even more critical is the need for and current lack of financial concepts and sponsorship for prototypical architectural and interior design, as well as modification and implementation of state-of-the-art hardware and technology, be it from the state, companies or health care sector.

The video of presentation is shown online:

People who use a highly interdisciplinary approach to start pathfinding and who utilize unorthodox methods of financial support are key to bridging these gaps and overcoming obstacles. When I first met Dr. Klaus Steinmeier-Bauer, one of the heads of business administration at Charité Facility Management (CFM), he introduced me to Prof. Claudia Spies from Charité – Universitätsmedizin Berlin and to her research and hypothesis on delirium. As a researcher into the causes and condition of "delirium", she has identified stress factors, such as noise pollution, distractions, the lack of a view, insufficient light and the lack of privacy, as important factors impacting the healing process and patient outcomes. A lack of daylight and insufficient lighting, for example, generally trigger fatigue and dizziness during the day, which causes sleep disorders at night.

Spies' intention was to find out how architectural improvements could help to support the medical outcomes of patients in health clinics in general, but more specifically in ICUs. Here, severely ill people would not only benefit most from such improvements but, even more importantly, it would create the right environment for detecting reliable outcomes and empirical data, since the position of the patients within the space is similar and comparable in any case. The viewing cones of patients can be predicted and acoustical data measured in relation to the position of the patient's head. With this in mind, the task was to design an environment that is carefully tailored to the patient's perception with an attempt to eliminate the above-mentioned stress-inducing elements, usually present in the design of healthcare facilities. It was necessary to keep the patient in a more familiar, soothing physical environment and within a natural circadian cycle as well as to effectively cater to the needs of caretakers in order to support a faster healing process and lower remission rates. Having worked for doctors all over the world, Claudia Spies was the first to believe that the architectural environment of a clinic could be more important than conventionally assumed. Since our first meeting, her thoughts on architecture-inducing stress factors, such as noise, lack of privacy, and lack of daylight to name just a few, have resulted in a wide range of architectural modifications to the ICU as we know it today.

2. From a Sketch to Interdisciplinary Research

The idea was not only to design but also to build a prototypical ICU environment to be used as a laboratory or testing environment. An initial sketch design by GRAFT in May 2011 already showed a concept for subtly hiding typical technical components in the architectural design, as well as new ideas for furniture components and a visionary ceiling featuring daylight-supporting LEDs combined with the potential for displaying a moving image. The main challenge, though, was not the generation of design ideas but rather the acquisition of funding for a research team that was needed to inform the design with the latest results on sleep and dream research, to investigate psychologically-relevant media content, and finally to develop the design into a realistic setup that could be built. Therefore, GRAFT submitted a grant application together with the Charité and Claudia Spies, and invited the media design company Art+Com and Prof. Joachim Sauter to join the group. Following consultations with specialists, ranging from sleep researchers to experts in lighting and acoustics from the Charité, the scientific research project "Parametrische (T)Raumgestaltung" (parametric dream [= TRAUM] / room [= RAUM] design) was born. With funding from the German Federal Ministry for Economic Affairs and Energy, a two-year process was initiated to de-

sign and supervise the implementation of two prototypical rooms in the ICU 8i ward on the Charité Virchow-Klinikum Campus in Berlin. Furthermore, the Charité and CFM pledged to finance a substantial part of the execution of the two rooms. These rooms have now been used as part of a three-year empirical study on the effects of a space on its inhabitants' behavior and patient outcomes. The rooms were completed in close collaboration with GRAFT and the medical staff at *Charité – Universitätsmedizin* Berlin, Germany. In the end, the project would have not been achieved without further generous sponsorship from the companies *Modultechnik* (mechanical equipment), van Bergh (furniture) and Philips (technical components and media screen execution).

3. Perception-Based Architecture for Contemporary Health Care Design

GRAFT's design creates an unexpected homely atmosphere through its soft and flowing forms, the use of large surfaces and dark wood floors. Special attention is placed on all of the visual "soft factors" of the space, the warm quality of the wood in indirect light, the unexpected dark color of the floor, and the seeming disappearance of technical equipment and supply lines. While arranged to suit the workflows of the medical staff, such equipment visually disappears from the patient's line of view. Alarm signals and noises caused by the equipment were shifted to the centrally-located observation room to improve acoustic conditions. Indirect light and individually-controlled lighting create a pleasant perception of space and light.

In order to support subjective impressions of "being in charge" instead of feeling lost and helpless, a patient lift facilitates the mobility of patients, while individually arrangeable furniture and view protectors enable ultimate privacy in the rooms. All technical equipment is hidden in a wooden "service wall" and disappears from the patient's view.

During the design phase, the main focus always remained on the patient's sensitivity and perception and, therefore, the central component of the concept is a large LED screen (2.4 m wide and up to 7 m in length) that is set up in the patient's field of view. The screen puts a primary focus on the usually underestimated surface of the ceiling above the patient. It allows not only the display of soothing and slowly changing images, but also acts as a supportive daylight simulation and interactive tool to support cognitive and physical exercise with the patient. The media screens and their integration in the spatial design of this ambitious research project are unique and unprecedented.

4. Postoperative Cognitive Dysfunctions and Architectural Perspectives

By reducing all detectable stress-inducing factors, such as noise, light, disorientation and the lack of privacy, the design is meant to enable a measurable improvement of the healing process and thus significantly reduce the occurrence of delirium and cognitive long-term damage.

The objective was to develop two pioneering intensive care rooms that would help to reduce fear, helplessness and stress through a holistic architectural approach. These were achieved two years later. The groundbreaking design was completed in October 2013.

The interior concept seeks to translate typical expectations and prejudices about ICUs into an inviting and welcoming atmosphere. The patient's perception and needs, and his or her

Fig. 1 Special attention has been placed on all of the visual "soft factors" of the space, the warm quality of the wood in indirect light, the unexpected dark color of the floor, and the seeming disappearance of technical equipment and supply lines. Image Credit: Tobias HEIN

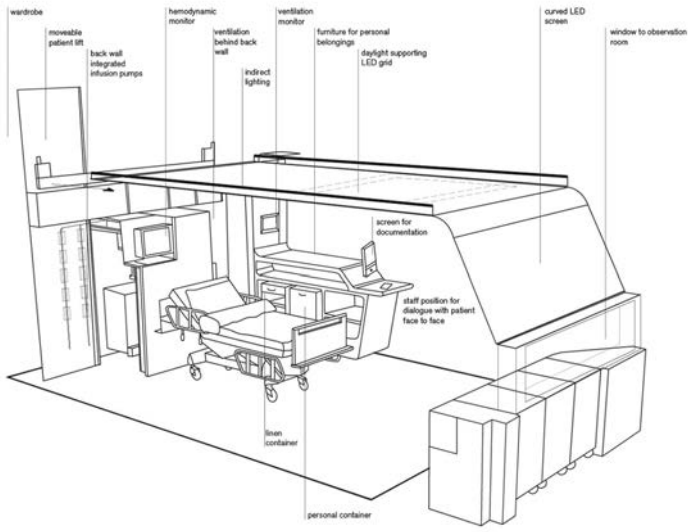

Fig. 2 Axonometry of the single bed setup. Image Credit: GRAFT GmbH

obvious feelings of helplessness and fear are the starting point for a revolutionary concept of strategically reducing the key stress factors mentioned above. Based on a number of identified parameters that cause stress and therefore affect performance and outcome of the treatment

in typical ICUs, the research program set up by Charité and GRAFT officially started in 2011 and will be concluded by clinical studies on the performance of the prototypical ICU in 2017. The room setup itself, as well as the software solution for the circadian lighting concept and media content are subject to two pending patents applied for by GRAFT, the Charité and Art+Com.

In recent years, the amount of admissions, as well as the average length of stay in ICUs has been rapidly increasing in part due to the demographic trend towards an older population, and the increasing number of environmentally triggered illnesses. Unlike the hospitality sector, the health care sector is interested in shortening hospital stays. Attempts to determine the factors which lead to a slow recovery process and to develop countermeasures, such as the Charité's collaboration with GRAFT to develop a prototype for the ICU of the future, have to continue and be extended to secure measurable results. It is therefore imperative that all parties involved, from the political stakeholders, to the insurance companies, operators of health care facilities, doctors and psychologists, join forces in supporting every effort into studying how architectural and space affect patient outcomes, not only for reasons of fiscal responsibility but, first and foremost, for the sake of our common interest.

Dipl.-Ing. Thomas Willemeit
GRAFT Berlin
Gesellschaft von Architekten mbH
Heidestraße 50
10557 Berlin
Germany
Tel.: +49 30 306451030
Fax: +49 30 3064510334
E-Mail: berlin@graftlab.com

Nova Acta Leopoldina NF Nr. *421*, 75–77 (2018)

Life-Priority

Jean-Daniel Chiche (Paris, France)

Abstract

About 8 million patients are treated in European Intensive Care Units (ICUs) every year. An adult will be admitted an average of 1.7 times to an ICU during his/her lifetime. The length of time a patient stays in intensive care depends on each individual patient case and can last from a few hours, to weeks or even months. Advances in intensive care medicine are therefore necessary.

Zusammenfassung

Über 8 Millionen Patienten werden jedes Jahr in europäischen Intensivstationen behandelt. Ein Erwachsener wird im Durchschnitt 1,7-mal in seinem Leben in eine Intensivstation eingewiesen. Die Länge der Zeit, die ein Patient in der Intensivstation verbringt, hängt von jedem einzelnen Patientenfall ab und kann von wenigen Stunden bis zu Wochen und sogar Monaten reichen. Fortschritte in der Intensivmedizin sind folglich erforderlich.

Each time our life is endangered, it is the intensive care team who takes care of us by supporting dysfunctional organs. We often picture intensive care as a temporary place, which is sometimes true, for example, when emergency intervention is vital in treating cardiac arrest. But it is also true that many patients remain in our units for longer periods of time, often weeks or more, to recover from organ dysfunction and to wait for their health to improve so that they can be transferred to wards where less one-on-one care is necessary. The length of time a patient stays in intensive care depends on each individual patient case and can last from a few hours, to weeks or even months. Advances must be made in intensive care to ensure that all other medical specialties progress. Each of us needs to become aware of how essential it is so that we can improve the future of intensive care medicine.

The video of presentation is shown online:

Fig. 1 The net of an Intensive Care Unit

– About 8 million patients are treated in European Intensive Care Units (ICUs) every year.
– An adult will be admitted an average of 1.7 times to an ICU during his/her lifetime. That means that every one of us has an appointment (or more than one!) with this special medical field.
– Global ICU mortality is roughly 20 %.
– According to evaluative scales, after a long stay in an ICU, the post-traumatic stress of a patient is five times higher than the stress of soldiers who have returned from a foreign mission.

Because intensive care workers prioritize our lives, let us give priority to intensive care. *Life-Priority* has three main goals in Europe:

– To raise money ...
  in order to finance research program, professional training, and initiatives which aim to further support intensive care patients and their families.

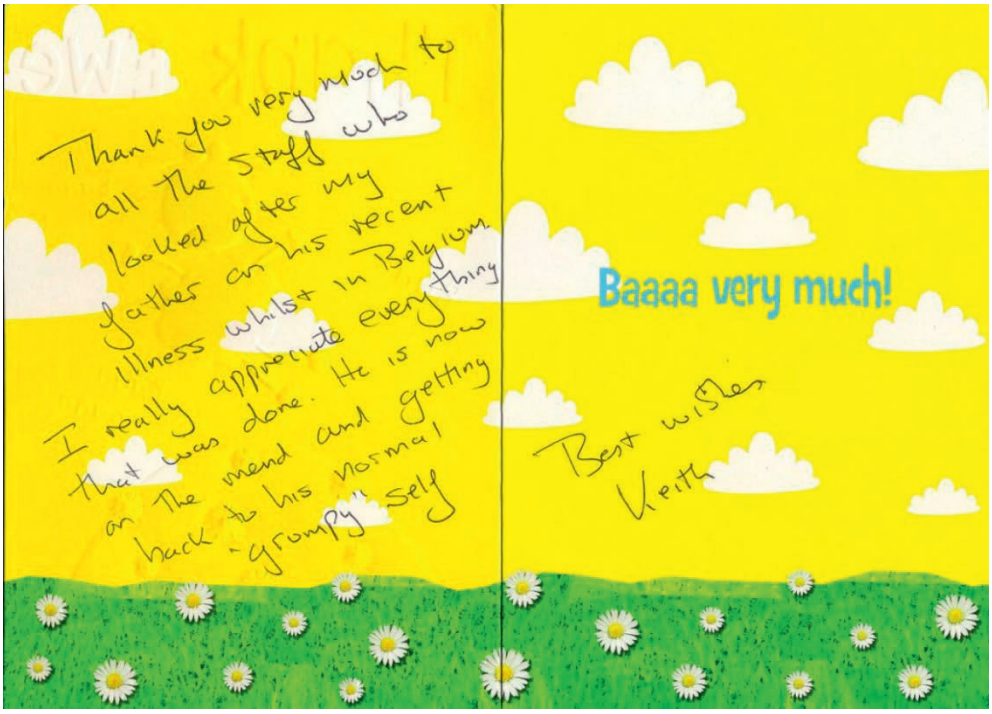

Fig. 2 Thanks for saving life

– To create awareness …
  among public institutions, companies, and the public of the importance of intensive care.
– To train …
  as many people as possible in the life-saving procedure of *cardiopulmonary resuscitation.*

Prof. Dr. Jean-Daniel Chiche
Life-Priority Fund, President
Réanimation Médicale – Hôpital Cochin
Université Paris Descartes
27 rue du Faubourg Saint-Jacques
75014 Paris
France
Tel.: +33 1 58412739
E-Mail: jean-daniel.chiche@cch.aphp.fr

Sleep Function and Dysfunction

Nova Acta Leopoldina NF Nr. *421*, 81–84 (2018)

Prevention of Delirium by a Modification in ICU Environment

Alawi Luetz (Berlin)

Abstract

Clinical trials investigating pharmacological delirium treatment and prevention strategies have failed to demonstrate consistent results in terms of patient outcomes. Hence, focus has moved towards non-pharmacological approaches. Within an interdisciplinary project, supported by the Federal Ministry of Economy, two ICU rooms were completely redesigned. The major goal of the redesigning process was to create a healing ICU environment that produces measurable improvements in the physical, cognitive and psychological states of patients. Beside interventions aimed at noise reduction, workflow optimization and infection control, we conducted modifications to improve lighting conditions in the room.

Zusammenfassung

Studien zur pharmakologischen Delirprävention und -therapie zeigen im Hinblick auf das Behandlungsergebnis von Intensivpatienten widersprüchliche Ergebnisse. Auch deswegen konzentriert sich die Forschung derzeit auf die Entwicklung nicht-pharmakologischer Behandlungsansätze. Im Rahmen eines interdisziplinären Forschungsprojektes, unterstützt vom Bundeswirtschaftsministerium, haben wir zwei Intensivbehandlungszimmer von Grund auf neu gestaltet. Das primäre Ziel der Neugestaltung war die Erschaffung einer Umgebung, die hinsichtlich physischer, kognitiver und psychologischer Gesundheit, messbare Verbesserungen im Behandlungsergebnis bedingt. Neben Maßnahmen zur Lärmreduktion, Verbesserung von Arbeitsabläufen und Infektionsprävention wurden Modifikationen der Lichtbedingungen im Raum durchgeführt.

In the next decade, the demand for Intensive Care Init (ICU) capacity is projected to grow rapidly because of an aging population. Elderly, critically ill patients are at an especially high risk of a prolonged ICU treatment and the development of long-term physical, psychological and cognitive disabilities. A recently published multicenter cohort study revealed that only 19 % of patients aged 66 years or older with an ICU length of stay (LOS) longer than two weeks were discharged directly from hospital to home. More importantly, 40 % of those patients died within the first year after ICU discharge. All surviving patients in this group suffered from severe and persistent functional dependencies. Cognitive dysfunction was observed more uniformly across all age groups (Herridge et al. 2016). This is in line with findings from a previous study showing that cognitive deficits occurred in one-third of both older and younger ICU patients, who had global cognition scores with a standard deviation of 1.5 below the population means (Pandharipande et al. 2013). A new cognitive, psychiatric

The video of presentation is shown online:

or physical disability, or worsening function after critical illness has been termed post-intensive care syndrome (PICS). Delirium is an acute and fluctuating disturbance in attention, awareness, and cognition. Results of numerous studies have revealed a prevalence of delirium ranging from 10 % up to 82 %. This acute form of brain dysfunction during ICU treatment often predicts long-term cognitive impairment and psychiatric diseases (Pandharipande et al. 2013, Jackson et al. 2014). Therefore, delirium prevention bundles have become an integral part of national and international guideline recommendations. Clinical trials investigating pharmacological strategies for the prevention and treatment of delirium have failed to demonstrate consistent results in terms of patient outcomes. Hence, focus has moved towards non-pharmacological approaches. One of the most important risk factors for transitioning to delirium is deep sedation. Furthermore, deep or moderate sedation during the first 48 hours of ICU treatment has been shown to predict increased mortality (Shehabi et al. 2012). That is why "the critically ill patient should be awake and alert [...]" (*Taskforce DAS* et al. 2015). However, this "no-sedation approach" is often challenging. Critically ill patients frequently suffer from symptoms of severe agitation during wakefulness which is mostly treated with sedatives. This agitation is often due to the stressful ICU environment. The feeling of being continuously monitored and exposed to different kinds of machinery or equipment, inadequate lighting and high sound pressure levels are major stressors. In this scenario, the ICU environment becomes an important modifiable risk factor for delirium.

Fig. 1 Photo of a modified ICU room at the Charité – Universitätsmedizin Berlin

We facilitated this approach of a "healing ICU environment" by redesigning two ICU rooms to reduce patient anxiety, helplessness and stress through a holistic architectural approach

(Fig. 1). Patient perceptions and needs were the starting point of this project. In this pilot project, supported by the German Ministry of Economics, two rooms were completely redesigned. The modular room concept consists of three functional components: lighting technology, medical technology and furniture. One key objective of the architectural modifications was noise reduction. We hypothesized that modifications of the room led to a significant decrease in sound pressure levels (SPLs) with fewer threshold overruns and a more pronounced day-night rhythm of SPLs. Initial study results show that SPLs were up to 10 decibels (dB) lower in the modified rooms compared to the standard rooms. During nighttime, the modification led to a significant decrease in 50 dB threshold overruns from 65.5 % to 10.5 %. Sound peaks of more than 60 dB were significantly reduced from 62.0 % to 26.7 %. Furthermore, we observed a significantly more distinct day-night pattern in the modified rooms with lower sound levels during nighttime (Luetz et al. 2016b). Sleep abnormalities and alterations in circadian melatonin secretion frequently occur in ICU patients and may trigger the development of delirium. Therefore, light therapy appears to be a promising way to reduce the incidence of these complications. In addition to implementing interventions aimed at noise shielding and a change in workflow, we made modifications to improve lighting conditions. We aimed at developing an artificial light source that is able to maintain or entrain the circadian rhythm of ICU patients. One integral part of the room is a new light-ceiling for each bed that extends from above the patient's head down to the patient's feet and covers an area of 15 square meters. In another experimental study we compared photometric parameters of the new LED ceiling with parameters of the standard light sources. We found that the newly developed LED-based light ceiling was the only light source that exceeded thresholds for maximal melatonin suppression in young and older adults without entering the range of absolute glare (Luetz et al. 2016a). We have yet to discover whether these technical improvements have any impact on patient outcomes. We are currently running the first prospective observational study to investigate whether patients treated in the modified rooms have less delirium than patients treated in the standard rooms. In addition to survival, the recovery process in intensive care should be clearly focused on long-term cognitive, psychiatric and functional outcomes. Besides technical requirements for organ support, the ICU environment should enable not only caregivers, but also the patients and their families to actively take part in the healing process. More interdisciplinary research is needed to develop and validate new concepts and technologies that help facilitate delirium prevention and recovery in critically ill patients.

References

Taskforce DAS, Baron, R., Binder, A., Biniek, R., Braune, S., Buerkle, H., Dall, P., Demirakca, S., Eckardt, R., Eggers, V., Eichler, I., Fietze, I., Freys, S., Fründ, A., Garten, L., Gohrbandt, B., Harth, I., Hartl, W., Heppner, H. J., Horter, J., Huth, R., Janssens, U., Jungk, C., Kaeuper, K. M., Kessler, P., Kleinschmidt, S., Kochanek, M., Kumpf, M., Meiser, A., Mueller, A., Orth, M., Putensen, C., Roth, B., Schaefer, M., Schaefers, R., Schellongowski, P., Schindler, M., Schmitt, R., Scholz, J., Schroeder, S., Schwarzmann, G., Spies, C., Stingele, R., Tonner, P., Trieschmann, U., Tryba, M., Wappler, F., Waydhas, C., Weiss, B., and Weisshaar, G.: Evidence and consensus based guideline for the management of delirium, analgesia, and sedation in intensive care medicine. Revision 2015 (DAS-Guideline 2015) – short version. Ger. Med. Sci. 2015;13:Doc19. doi: 10.3205/000223. eCollection 2015

Herridge, M. S., Chu, L. M., Matte, A., Tomlinson, G., Chan, L., Thomas, C., Friedrich, J. O., Mehta, S., Lamontagne, F., Levasseur, M., Ferguson, N. D., Adhikari, N. K. J., Rudkowski, J. C., Meggison, H., Skrobik, Y., Flannery, J., Bayley, M., Batt, J., Santos, C. D., Abbey, S. E., Tan, A., Lo, V., Mathur, S.,

Parotto, M., Morris, D., Flockhart, L., Fan, E., Lee, C. M., Wilcox, M. E., Ayas, N., Choong, K., Fowler, R., Scales, D. C., Sinuff, T., Cuthbertson, B. H., Rose, L., Robles, P., Burns, S., Cypel, M., Singer, L., Chaparro, C., Chow, C. W., Keshavjee, S., Brochard, L., Hebert, P., Slutsky, A. S., Marshall, J. C., Cook, D., Cameron, J. I., *RECOVER*, *Program Investigators* (Phase 1: towards RECOVER) & *Canadian Critical Care Trials Group*: The recover program: Disability risk groups and 1-year outcome after 7 or more days of mechanical ventilation. Amer. J. Respir. Crit. Care Med. *194*/7, 831–844 (2016)

Jackson, J. C., Pandharipande, P. P., Girard, T. D., Brummel, N. E., Thompson, J. L., Hughes, C. G., Pun, B. T., Vasilevskis, E. E., Morandi, A., Shintani, A. K., Hopkins, R. O., Bernard, G. R., Dittus, R. S., Ely, E. W., and *Bringing to Light the Risk Factors and Incidence of Neuropsychological Dysfunction in ICU Survivors (BRAIN-ICU) Study Investigators*: Depression, post-traumatic stress disorder, and functional disability in survivors of critical illness in the brain-icu study: a longitudinal cohort study. Lancet Respir. Med. *2*/5, 369–379 (2014)

Luetz, A., Piazena, H., Weiss, B., Finke, A., Willemeit, T., and Spies, C.: Patient-centered lighting environments to improve health care in the intensive care unit. Clin. Health Promot. *6*/1, 5–12 (2016a)

Luetz, A., Weiss, B., Penzel, T., Fietze, I., Glos, M., Wernecke, K. D., Bluemke, B., Dehn, A. M., Willemeit, T., Finke, A., and Spies, C.: Feasibility of noise reduction by a modification in ICU environment. Physiol. Meas. *37*/7, 1041–1055 (2016b)

Pandharipande, P. P., Girard, T. D., Jackson, J. C., Morandi, A., Thompson, J. L., Pun, B. T., Brummel, N. E., Hughes, C. G., Vasilevskis, E. E., Shintani, A. K., Moons, K. G., Geevarghese, S. K., Canonico, A., Hopkins, R. O., Bernard, G. R., Dittus, R. S., Ely, E. W., and *BRAIN-ICU Study Investigators*: Long-term cognitive impairment after critical illness. New Engl. J. Med. *369*/14, 1306–1316 (2013)

Shehabi, Y., Bellomo, R., Reade, M. C., Bailey, M., Bass, F., Howe, B., McArthur, C., Seppelt, I. M., Webb, S., Weisbrodt, L., *Sedation Practice in Intensive Care Evaluation (SPICE) Study Investigators* and *ANZICS Clinical Trials Group*: Early intensive care sedation predicts long-term mortalityin ventilated critically ill patients. Am. J. Respir. Crit. Care Med. *186*/8, 724–31 (2012)

PD Dr. med. Alawi Luetz
Department of Anaesthesiology and
Intensive Care Medicine
Campus Charité Mitte
and Campus Virchow-Klinikum
Charité – Universitätsmedizin Berlin
Charitéplatz 1
10117 Berlin
Germany
Tel.: +49 30 450531208
Fax: +49 30 450531911
E-Mail: alawi.luetz@charite.de

Nova Acta Leopoldina NF Nr. *421*, 85 – 89 (2018)

Delirium and Circadian Integrity

Margaret Pisani (New Haven, CT, USA)

Abstract

Delirium in the Intensive Care Unit (ICU) is common in critically ill patients and has a major impact on outcomes. There is assumed to be a relationship between sleep deprivation and delirium since circadian rhythm abnormalities likely contribute to delirium, altered mentation, impaired immunity, autonomic dysfunction, and endocrine abnormalities that result from disruptions to the sleep-wake cycle and impairment to the central nervous system. Factors contributing to circadian disruption include bright lights at night, noise, in-room interruptions and medication. It is the task to find a systemic approach which focuses on pathophysiological mechanisms and sleep interventions that improve outcomes for our ICU patients.

Zusammenfassung

Delirium auf der Intensivstation ist weitverbreitet bei schwerkranken Patienten und hat eine bedeutende Auswirkung auf die Behandlungserfolge. Es wird angenommen, dass eine Beziehung zwischen Schlafmangel und Delirium besteht, da Unregelmäßigkeiten beim Biorhythmus wahrscheinlich zum Delirium, zu einer veränderten Denktätigkeit, zu einer geschwächten Immunität, zu einer autonomen Funktionsstörung und zu Unregelmäßigkeiten im Hormonhaushalt, die sich aus Störungen im Schlaf-Wach-Rhythmus und Beeinträchtigungen des zentralen Nervensystems ergeben, beitragen. Faktoren, die zu Störungen im Biorhythmus führen, umfassen helle Lichter bei Nacht, Lärm, Störungen im Zimmer und Medikamente. Die Aufgabe ist, einen systemischen Ansatz zu finden, der sich auf pathophysiologische Mechanismen und Schlafinterventionen konzentriert, die die Behandlungserfolge unserer Intensivpatienten verbessern.

1. Delirium – Definition and Importance

The 5th edition of the *American Psychiatric Association's Diagnostic and Statistical Manual* (DSM-V) defines delirium as a clinical syndrome characterized by an acute onset of a fluctuating disturbance in attention and cognition in the setting of pathophysiological stressors which is not better explained by a pre-existing, established, or evolving neurocognitive disorder. Additional features include psychomotor behavioral disturbances, such as hypoactivity or hyperactivity, and impairment in sleep duration and architecture.

The video of presentation is shown online:

Delirium is especially common in critically ill patients, with prevalence rates dependent on the patient population. Rates are between 50 – 90 % in older intensive care patients. Several studies have demonstrated that delirium in the Intensive Care Unit (ICU) is independently associated with increased mortality, length of hospital stay, poorer functional outcomes and increased hospitalization costs. Numerous risk factors for delirium have been identified in epidemiological studies and include increased age, pre-existing cognitive impairment, poor functional status, sensory impairment, electrolyte disturbances and medication use.

There is an observed overlap in the symptoms of sleep deprivation and delirium which include abnormalities in attention, level of consciousness and cognitive performance. Although no direct biological relationship has been established between delirium and sleep deprivation, it seems probable, based on their shared epidemiological, biochemical and anatomical similarities, that these two conditions are clinically related.

2. Circadian Rhythms – Definition and Disruption

Circadian rhythms are biological cycles that follow a 24-hour periodicity. Most cells in the body express clock-related genes that govern the activity of about one-third of all genes. Circadian rhythms are regulated by three key components: (*a*) an entrainment system, (*b*) a central pacemaker found in the suprachiasmatic nucleus and (*c*) effector systems that regulate biological rhythms. In humans, the environmental time-signaling stimuli include light, social cues, physical activity and nutrition, with light being the strongest *zeitgeber* (environmental time-signaling stimulus). Light influences the release of melatonin from the pineal gland and helps to entrain secondary biological clocks throughout the body. Circadian rhythm is synchronized with day and night, and circadian variables exhibit a certain magnitude of fluctuation (amplitude) and peak time (acrophase).

Light is the primary cue which signals the master clock (★) to coordinate physiological processes throughout the body (entrainment). The master clock uses melatonin secretion to coordinate peripheral clocks that are present in all organs. Abnormalities in the circadian rhythm likely contribute to delirium by distrupting the sleep-wake cycle and impairing the central nervous system.

In critical illness, circadian rhythms are disrupted both in terms of abnormal amplitude and phase shifting. Circadian disruption can clinically contribute to altered mentation, impaired immunity, autonomic dysfunction and endocrine abnormalities. The sleep-wake cycle disturbance often observed with delirium can be considered a circadian rhythm disturbance.

There are multiple potential environmental factors in the ICU that contribute to circadian disruption including bright light at night and dim light during the day, noise, in-room interruptions, medications, bedrest, and continuous tube feeds. In addition, patient factors, such as the critical illness (inflammatory mechanisms), psychological distress and pain, contribute to abnormalities in circadian rhythms.

3. Delirium and Circadian Disruption

There is biological plausibility for presuming there is a relationship between circadian disruption and delirium. Evidence for this biological link can be found in the overlap of a variety of

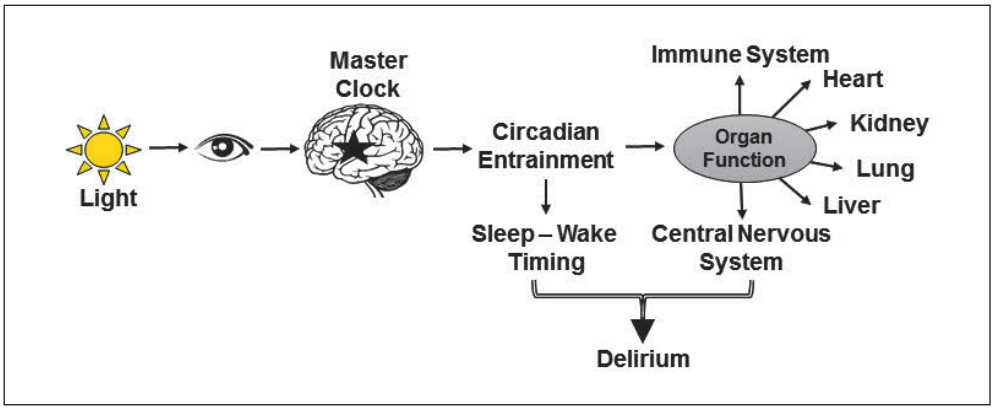

Fig. 1 Model of the circadian system

basic biological and clinical neurotransmitter studies on circadian biology and delirium. The implicated pathways include cholinergic, dopaminergic, GABAergic, melatonergic, tryptophan, serotonin and the hypothalamic-pituitary-adrenal (HPA) axis. In addition, there is some evidence that inflammatory mechanisms may explain a linkage between circadian disruption and delirium.

Possible mechanisms that may explain the relationship between delirium and circadian disruption are presented in Table 1.

Tab. 1 Theories explaining the relationship between circadian mechanisms and delirium

– Disruption of circadian systems may account for the disturbed sleep-wake cycle, motor hyper/hypo activity, impaired cognition and fluctuation of symptoms seen in delirium.
– Delirium contributes to circadian dysregulation by impacting one's ability to comprehend and interact with the environment, resulting in an uncoupling of circadian entrainment mechanisms.
– Delirium is a primary circadian rhythm disorder. The disturbance of circadian rhythm then causes the impaired cognition and neuropsychiatric symptoms seen with delirium.
– Delirium and circadian rhythm disruption are discrete syndromes that share certain symptoms. They increase the likelihood of the other occurring and are mutually aggravating.
– Circadian disruption occurs with specific risk factors such as increasing age, dementia and medication use. These risk factors also predispose a patient to delirium.
– Delirium and circadian rhythm disruption occur together by chance and are reflective of a loss of physiological reserves in older patients or those with dementia.

Circadian disruption (Tab. 2) has been demonstrated in critically ill patients and seems grossly proportional to the severity of illness. Observational studies of circadian rhythm in the ICU have used vital signs such as temperature, blood pressure, heart rate and ventilator equivalents. There are also studies which have examined hormones including melatonin, cortisol, adrenocorticotropic hormone (ACTH) and leptin. The cytokines studied include tumor necrosis factor (TNF), interleukin-6 (IL-6) and interleukin-13 (IL-13).

Tab. 2 Circadian rhythm disruption in the critically ill

– Sleep-wake cycles – Melatonin – Autonomic indices – Core body temperature – Cortisol

Other studies have examined clinical deterioration, glucose patterns and clock gene expression in ICU patients. Despite these studies, the directionality of the relationship between delirium, brain dysfunction, sleep loss, circadian misalignment, and critical illness is not known.

4. Future Directions

A research agenda for delirium prevention and treatment should include studies on the pathogenesis of delirium using animal models, human studies and objective measures. We need a better understanding of the many potential underlying mechanisms to be able to refine our current approaches to the diagnosis, prevention and treatment of delirium. In addition, the link between sleep interventions, improved sleep, and outcomes need to be studied using sleep intervention and objective measures of improved sleep along with an assessment of the clinical outcomes, including delirium. Due to the complexity of the relationship between critical illness, sleep and delirium, prospective studies examining the impact of sleep interventions should occur in settings where protocols exist and guideline-recommended practices are carried out with regard to sedation use, mobilization, and prevention and treatment of delirium. This will allow us to test for the impact of a sleep intervention on delirium.

A systematic approach is necessary to evaluate the complex link between circadian disruption, sleep and delirium. Research efforts that employ interdisciplinary and multidisciplinary approaches are likely to yield the most promising strategies for untangling the relationship between delirium pathogenesis and circadian disruption.

Selected References

Brainard, J., Gobel, M., Bartels, K., Scott, B., Koeppen, M., and Eckle, T.: Circadian rhythms in anesthesia and critical care medicine: Potential importance of circadian disruptions. Sem. Cardithorac. Vasc. Anesth. *19*/1, 49–60 (2015)

deRooij, S. E., and van Munster, B. C.: Melatonin deficiency hypothesis in delirium: A synthesis of current evidence. Rejuvenation Research *16*/4, 273–278 (2013)

Fitzgerald, J. M., Adamis, D., Trzepacz, P. T., O'Regan, N., Timmons, S., Dunne, C., and Meagher, D. J.: Delirium: A disturbance of circadian integrity. Medical Hypothesis *81*, 568–576 (2013)

Flannery, A. H., Oyler, D. R., and Weinhouse, G. L.: The impact of interventions to improve sleep on delirium in the ICU: A systematic review and research framework. Crit. Care Med. *44*, 2231–2240 (2016)

Fung, C. H., Vitiello, M. V., Alessi, C. A., and Kuchel, G. A.: Report and research agenda of the American Geriatrics Society and National Institute on Aging Bedside-to-Bench Conference on sleep, circadian rhythms, and aging: New avenues for improving brain health, physical health, and functioning. JAGS 2016

Kamdar, B. B., Niessen, T., Colantuoni, E., King, L. M., Neufeld, K. J., Bienvenu, O. J., Rowden, A. M., Collop, N. A., and Needham, D. M.: Delirium transitions in the medical ICU: Exploring the role of sleep quality and other factors. Crit. Care Med. *43*, 135–141 (2015)

Knauert, M. P., Haspel, H. A., and Pisani, M. A.: Sleep loss and circadian rhythm in the intensive care unit. Clin. Chest. Med. *36*/3, 419–429 (2015)

Oldham, M. A., Lee, H. B., and Desan, P. H.: Circadian rhythm disruption in the critically ill: An opportunity for improving outcomes. Crit. Care Med. *44*/1, 207–217 (2016)

Patel, J., Baldwin, J., Bunting, P., and Laha, S.: The effect of a multicomponent multidisciplinary bundle of interventions on sleep and delirium in medical and surgical intensive care patients. Anesthesia *69*, 540–549 (2014)

Margaret Pisani, MD, MPH
Yale University School of Medicine
Pulmonary, Critical Care & Sleep Medicine
PO Box 208057
300 Cedar Street
New Haven, CT 06520-8057
USA
Tel.: +1 203 7853207
Fax: +1 203 7853826
E-Mail: margaret.pisani@yale.edu

Nova Acta Leopoldina NF Nr. *421*, 91–93 (2018)

Melatonin: Panacea or Futile Hope?

Kotaro Hatta (Tokyo, Japan)

Abstract

Delirium is related to sleep-wake cycle disturbances which include insomnia, excessive daytime napping and the disintegration of expected circadian rhythms. The sleep-wake cycle is regulated by the hormone melatonin, which is excreted by the pineal gland. Current literature suggests that melatonin prophylaxis may reduce the incidence and severity of delirium. Ramelteon, a melatonin receptor agonist, was recently shown to protect acute care patients against delirium when administered nightly. The task is to strengthen these results in multicentric studies and to implement the protocol in clinical routines to improve patient-centered outcomes.

Zusammenfassung

Delirium ist mit Störungen im Schlaf-Wach-Rhythmus verbunden, die Insomnie, übermäßigen Tagschlaf und das Auseinanderfallen des erwarteten Biorhythmus einschließen. Der Schlaf-Wach-Rhythmus wird durch das Hormon Melatonin gesteuert, das von der Epiphyse gebildet wird. Aktuelle Literatur verweist darauf, dass eine Melatoninprophylaxe das Auftreten und die Stärke eines Deliriums reduzieren kann. Für Ramelteon, einen Melatonin-Rezeptor-Agonist, wurde kürzlich gezeigt, dass bei einer nächtlichen Verabreichung damit Akutpatienten gegen Delirium geschützt werden. Die Aufgabe ist, diese Ergebnisse in multizentrischen Studien stärker herauszuarbeiten und das Protokoll im Klinikalltag zur Verbesserung der patientenorientierten Erfolgsbewertung umzusetzen.

The basic definition of delirium is altered arousal (*European Delirium Association and American Delirium Society* 2014). For decades, sleep-wake cycle disturbances, including insomnia, excessive daytime napping and disintegration of the expected circadian patterns, have been described as characteristic components of delirium and identified as the core symptoms of delirium (Maldonado 2013). Melatonin, a pineal gland hormone, regulates the sleep-wake cycle and some emerging literature suggests that melatonin prophylaxis may reduce the incidence of delirium or long-lasting episodes of delirium (Sultan 2010, Al-Aama et al. 2011, de Jonghe et al. 2014). Sultan (2010) reported that after medications were given orally 90 min before the operation and at sleep time on the night of the operation, there was a statistically significant drop in the percentage of postoperative delirium in the melatonin group down to 9.43 % (5/53 patients) compared with the control group (32.65 % [16/49], relative risk 0.29, $P = .0062$). Al-Aama et al. (2011) reported that melatonin (0.5 mg every night for 14 days or until discharge) was associated with a lower risk of delirium (12.0 % versus 31.0 % [placebo],

The video of presentation is shown online:

P = .014), with an Odds Ratio (OR), adjusted for dementia and co-morbidities, of 0.19. De Jonghe et al. (2014) reported that although melatonin (3 mg in the evening for 5 consecutive days) did not affect the incidence of delirium (29.6 % in the melatonin group [55/186 patients scheduled for acute hip surgery] versus 25.5 % in the placebo group [49/192]), a smaller proportion of patients in the melatonin group experienced a long-lasting episode of delirium (> 2 days) than in the placebo group (25.5 % versus 46.9 %; P = .02).

In a multicenter, rater-blinded, randomized placebo-controlled clinical trial, we examined whether ramelteon, which is a melatonin agonist whose affinities for melatonin 1 (MT_1) and melatonin 2 (MT_2) receptors are 6- and 3-fold higher respectively than those of melatonin, can effectively prevent delirium (Hatta et al. 2014). Eligible patients were 65 – 89 years old who had recently been admitted in an emergency to intensive care units and regular acute care wards in four university hospitals and one general hospital, and who were able to take medicine orally. Patients were excluded from the study if their expected stay or life expectancy was less than 48 h. Using the sealed envelope method, 67 patients were randomly assigned to receive ramelteon (8 mg/day; n = 33) and a placebo (n = 34) every night for 7 days. The main outcome measure was incidence of delirium as determined by the *Diagnostic and Statistical Manual of Mental Disorders* IV Text Revision (DSM-IV-TR). Ramelteon was associated with a lower risk of delirium (3 % versus 32 %, P =.003) and with a relative risk of 0.09 (95 % confidence interval [CI], 0.01–0.69). Even after controlling for risk factors such as age, dementia and diagnosis of an infection at the time of admission, ramelteon was still associated with a lower incidence of delirium (P =.01; odds ratio, 0.07; 95 % CI, 0.008 – 0.54). Kaplan-Meier estimates the time until the development of delirium to be 6.94 days (95 % CI, 6.82–7.06 days) for ramelteon and 5.74 days (5.05 – 6.42 days) for the placebo. A log-rank test comparison showed that the frequency of developing delirium was significantly lower in patients taking ramelteon than in those taking the placebo (χ^2 = 9.83, P = .002). Furthermore, ramelteon was associated with a lower risk of delirium among patients with a clinical dementia rating (CDR) ≥ 0.5 (6 % for the ramelteon group versus 62 % for the placebo group, P =.003), with a relative risk of 0.15 (95 % CI, 0.02–0.96) (Hatta et al. 2015). These findings suggest that ramelteon, administered nightly to elderly patients admitted for acute care, protects against delirium, and they support a possible pathogenic role of melatonin neurotransmission in delirium. One limitation in clinical practice, especially in an intensive care situation, is the lack of intravenous formulations of melatonin and its agonists.

Another possible mechanism that melatonin and ramelteon have for preventing delirium, other than an improvement in the sleep-wake cycle, is their anti-microbial properties. Fink et al. (2014) reported that survival rates in rats that experimentally developed sepsis significantly improved after the administration of 1.0 mg/kg of ramelteon or melatonin, compared with vehicle-treated animals, and that coadministration of the melatonin receptor-antagonist luzindole abolished this effect completely. As infection is a clinical factor that might precipitate delirium (Young et al. 2010), anti-septic effects of melatonin and ramelteon might be associated with the effects of preventing delirium. This finding can be partially explained by the change in balance between two pathways of tryptophan metabolism when there is inflammation. Tryptophan is metabolized through two major pathways: the kynurenine pathway and the methoxyindole pathway. The methoxyindole pathway generates serotonin, which is a further substrate for melatonin biosynthesis. The kynurenine pathway can be activated by inflammatory stimuli (Lovelace et al. 2017). This change in the balance between the two pathways of tryptophan metabolism can decrease in melatonin biosynthesis. Therefore, giving

melatonin or ramelteon to patients with systemic inflammation, which may cause delirium, can compensate for a lack of melatonin, resulting in the prevention of delirium.

In clinical practice, we first choose ramelteon to treat insomnia in elderly patients and to prevent delirium from developing. Thus, the potent melatonin agonist ramelteon plays an important role, not only in fighting insomnia, but also in preventing delirium.

References

Al-Aama, T., Brymer, C., Gutmanis, I., Woolmore-Goodwin, S. M., Esbaugh, J., and Dasgupta, M.: Melatonin decreases delirium in elderly patients: a randomized, placebo-controlled trial. Int. J. Geriatr. Psychiatry *26*/7, 687–694 (2011)

European Delirium Association and American Delirium Society: The DSM-5 criteria, level of arousal and delirium diagnosis: inclusiveness is safer. BMC Med. *12*, 141 (2014)

Fink, T., Glas, M., Wolf, A., Kleber, A., Reus, E., Wolff, M., Kiefer, D., Wolf, B., Rensing, H., Volk, T., and Mathes, A. M.: Melatonin receptors mediate improvements of survival in a model of polymicrobial sepsis. Crit. Care Med. *42*/1, e22–31 (2014)

Hatta, K., Kishi, Y., and Wada, K.: Ramelteon for delirium in hospitalized patients. JAMA *314*/19, 1071–1072 (2015)

Hatta, K., Kishi, Y., Wada, K., Takeuchi, T., Odawara, T., Usui, C., Nakamura, H., and *DELIRIA-J Group*: Preventive effects of ramelteon on delirium: a randomized placebo-controlled trial. JAMA Psychiatry *71*/4, 397–403 (2014)

Jonghe, A. de, van Munster, B. C., Goslings, J. C., Kloen, P., van Rees, C., Wolvius, R., van Velde, R., Levi, M., Haan, R. J. de, Rooij, S. E. de, and *Amsterdam Delirium Study Group*: Effect of melatonin on incidence of delirium among patients with hip fracture: a multicentre, double-blind randomized controlled trial. Canad. Med. Assoc. J. (CMAJ) *186*/14, E547–556 (2014)

Lovelace, M. D., Varney, B., Sundaram, G., Lennon, M. J., Lim, C. K., Jacobs, K., Guillemin, G. J., and Brew, B. J.: Recent evidence for an expanded role of the kynurenine pathway of tryptophan metabolism in neurological diseases. Neuropharmacology *112*, 373–388 (2017), doi: 10.1016/j.neuropharm.2016.03.024. [Epub ahead of print]

Maldonado, J. R.: Neuropathogenesis of delirium: review of current etiologic theories and common pathways. Amer. J. Geriatr. Psychiatry *21*/12, 1190–1222 (2013)

Sultan, S. S.: Assessment of role of perioperative melatonin in prevention and treatment of postoperative delirium after hip arthroplasty under spinal anesthesia in the elderly. Saudi J. Anaesth. *4*/3, 169–173 (2010)

Young, J., Murthy, L., Westby, M., Akunne, A., O'Mahony, R., and *Guideline Development Group*: Diagnosis, prevention, and management of delirium: summary of NICE guidance. Brit. Med. J. *341*, c3704 (2010)

Prof. Kotaro Hatta, MD, PhD
Department of Psychiatry
Juntendo University
Nerima Hospital
3-1-10 Takanodai
Nerima-ku
Tokyo 117-8521
Japan
E-Mail: khatta@juntendo.ac.jp

Nova Acta Leopoldina NF Nr. *421*, 95 – 99 (2018)

Evidence Gap to the Ideal Patient-Centered Care

Yahya Shehabi (Melbourne, Australia)

Abstract

Clinicians commonly focus on short-term outcomes when the priority is to preserve life. However, organ damage, especially in neuronal cells and the brain, may persist long after vital signs have been corrected. This constitutes the greatest gap in current intensive care that needs to be bridged in order to improve long-term and short-term outcomes. Our interventions preserve life but fail to prevent long-term suffering in our patients and their families. We therefore need a new intensive care infrastructure, a workforce focused on harm avoidance, family engagement, early physical therapy, sleep promotion and a high level of evidence for the most effective interventions, which is currently lacking.

Zusammenfassung

Krankenhausärzte konzentrieren sich üblicherweise auf kurzzeitige Resultate, wenn die Priorität darin besteht, Leben zu erhalten. Dennoch können Organschäden, insbesondere in neuronalen Zellen und dem Gehirn fortbestehen, lange nachdem die Vitalparameter wieder eingestellt worden sind. Darin besteht die große Kluft in der derzeitigen Intensivpflege, die geschlossen werden muss, um Lang- und Kurzzeitergebnisse zu verbessern. Unsere Interventionen erhalten Leben, aber vermeiden auf längere Sicht das Leiden unserer Patienten und ihrer Familien nicht. Daher benötigen wir eine neue Infrastruktur für die Intensivpflege, eine Belegschaft, die sich darauf konzentriert, Leid zu vermindern, ein familiäres Engagement, eine frühzeitige Physiotherapie, eine Schlafförderung und einen deutlichen Evidenzbeleg für die effektivsten Interventionen, welcher derzeit noch fehlt.

1. ICU Doctors, Patients and Their Families – Are We on the Same Page?

Norman was 62 when he underwent emergency surgery for a perforated colon. The surgery was complicated and resulted in severe sepsis, acute kidney injury, agitated delirium and respiratory failure. He was heavily sedated during the first five days following surgery, ventilated for nine days and needed prolonged vasopressor infusions and four weeks of dialysis before he was finally discharged from the Intensive Care Unit (ICU).

The video of presentation is shown online:

Norman was self-employed, lived with his wife and had three children. His wife was a teacher. When doctors explained Norman's clinical status after surgery, she asked whether he was likely to make it. How long before he could leave hospital? Would he have any remaining weakness? Was there any risk of brain damage? If all goes well, how long before he would be able to return to work? Her questions focused on life after the ICU and revealed the need for a long-term perspective. Although not often stated, it is a view shared by most families of patients who suffer critical illness.

At the bedside, however, clinicians focused on fixing measurable things, like blood pressure, heart rate, oxygenation, urine output and the like. Beside the tangible, immediately anticipated response to treating physiological measures, such as blood pressure (for example through the infusion of a vasopressor), there is a belief among ICU clinicians that these variables reflect the life threatening elements of critical illness and thus priority should primarily be placed on correcting them and returning them to normal physiological values.

The contrast in perspectives could not be starker. Doctors and ICU caregivers have a short-term focus that prioritizes preservation of life. What happens after ICU discharge is someone else's problem. Many would say we do not know better, this is the limit of our knowledge and skills. We deliver what we are good at. For Norman's wife and their children, however, this was not enough. This viewpoint explores the gaps and the bridges that need to be crossed in order to deliver holistic care, one that not only preserves life, but improves Norman's outcomes and those of many critically ill patients in our ICUs.

2. Delivering a Common Goal

Advances in cardiovascular, pulmonary and vital organ support have made the task of correcting low blood pressure or improving a patient's oxygenation relatively straightforward in most cases of critical illness. While it is important to maintain the supply of oxygen to vital organs, clinicians and caregivers in ICUs face the task of dealing with organ damage which may persist long after vital signs have been corrected. Of primary importance are neuronal cells which are widely distributed centrally and peripherally and play a vital role in the long-term outcomes of patients who survive the ICU. In critical illness, the brain is the real victim and inside the closed box, as doctors refer to it, the brain suffers in silence.

3. Can We Do Better? The Need for a Different Focus

Early in the 21st century, delirium – perhaps an obvious sequela of an insult to the brain – emerged as a significant component of critical illness. The Confusion Assessment Method (CAM) was modified for intensive care patients, and the CAM-ICU became a commonly used tool to diagnose delirium. Early reports linked delirium to prolonged ventilation time, increased hospital and ICU stays and mortality. A subsequent report also linked delirium to long-term cognitive decline, depression and other psycho-social disorders. A heightened focus on delirium was therefore justified.

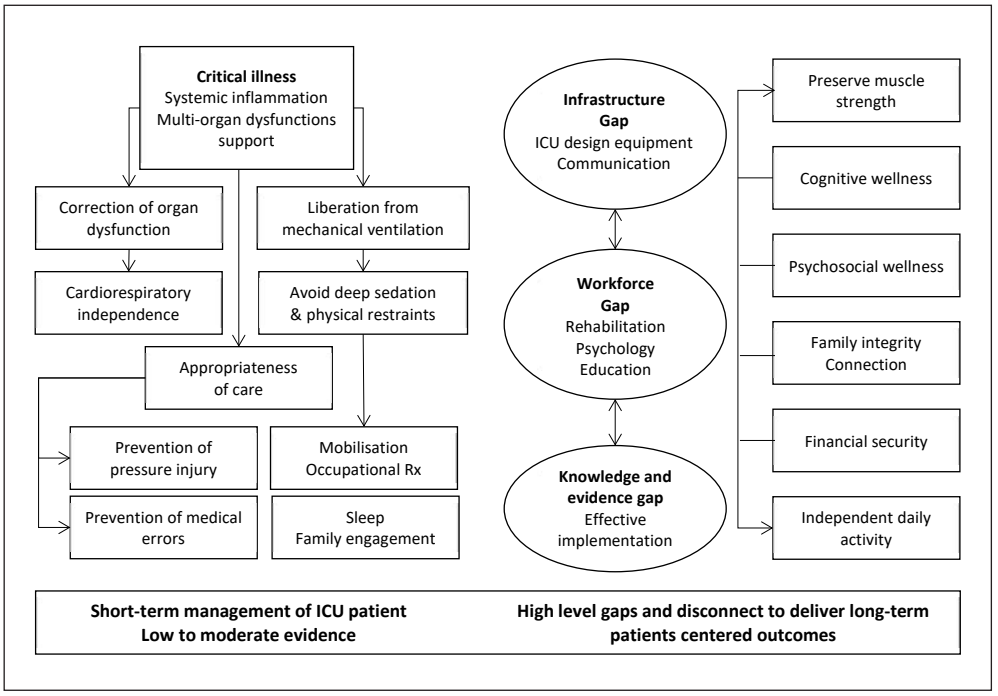

Fig. 1 A three-dimensional approach is needed

While many would agree that 15 years of delirium-ology improved our recognition, understanding and, to a lesser degree, our management of delirium, there has been no documented or reported improvement in patient-centered short or long-term outcomes. There is a consensus that delirium is bad and should be identified, prevented and treated – if we know how. This is only one example, a very good one, where the focus is on simple solutions to complex problems. These are often attractive but universally wrong.

Clinicians remain focused on the short term. Eminent societies and colleges have issued various clinical practice guidelines on sedation, sepsis, and liberation from mechanical ventilation. Multiple bundles, such as the awakening, breathing coordination, choice of drugs, delirium management and family engagement (known as ABCDE/F) and the early provision of comfort using analgesia, minimal sedation and humane care (known as eCASH), as well as other protocoled sedation bundles have also been proposed to improve patient outcomes in the ICU. Despite the strong support by the proponents of these guidelines and bundles of care, the evidence behind most of these interventions is either low or at best circumstantial. As such, its implementation and uptake remain incomplete and, most importantly, its impact on patient-reported long-term outcomes is unknown.

Despite our advances in knowledge and technology, patients ventilated for more than 48 hours continue to suffer, for up to one year after discharge, immense negative neurological and psychosocial effects that are synonymous with civilians and soldiers exposed to the trauma of war. Thus, our interventions, although they may have preserved life, have failed to prevent the long-term suffering of our patients and their families.

4. We Need a New Infrastructure for Intensive Care

Intensive care was established in the early 1950s serving as respiratory support units in the peak of the polio epidemic. Over the next fifty years, intensive care practice evolved to become one of the most successful and independent specialties. The design of ICUs moved towards bigger and larger units, however, the focus remained on isolated vital organ support. There is an urgent need to change the focus of ICU infrastructure to reflect the holistic, comprehensive patient- and family-centered long-term goals after ICU.

Future ICUs should be designed to:

- Respect the privacy and beliefs of patients and their families.
- Allow for maximum interaction and engagement with families.
- Allow time and personal orientation via communication and visual orientation.
- Reduce noise.
- Allow changing light patterns to reflect changes in day/night, which promote sleep.
- Have the necessary equipment to allow easy mobilization and occupational therapy.
- Embrace modern communication to enhance distant and remote engagement with family members unable to visit, and to keep up with favorite sports teams.

5. We Need an Augmented Workforce for Intensive Care

Traditionally, the intensive care workforce included medical and nursing practitioners. Although many hospitals have expanded the ICU workforce to include physiotherapists, dieticians and clinical pharmacists, there is a need for an augmented workforce that is capable of delivering aspects of care that could impact long-term outcomes. Appropriate trained physical and occupational therapists, supported by proper equipment, would form a mobility team that would encourage early access to mobilization and physical rehabilitation.

In addition, the training of bedside caregivers should also focus on improving their understanding of the long-term goals of ICU patients and to implement strategies that could enhance and make use of modern, purpose-built ICUs to deliver short- and long-term patient-centered outcomes. These strategies include harm avoidance, family engagement, the encouragement of early physical therapy and sleep promotion.

6. We Need High-Level Evidence for the Most Effective Interventions

An important, non-isolated hurdle in the delivery of patient-centered care is the lack of high-level evidence for many of the interventions used in ICUs, particularly for interventions that impact long-term quality of life. There is an urgent need to conduct trials that focus on candidate interventions to reverse the impact of critical illness on muscle strength and activity, neuronal activation and subsequent cognitive injury.

As for our patient Norman, he was discharged from the hospital after 43 days, still suffering from significant muscle weaknesses and was still not back to work 14 months after discharge. His family is hoping for improvement in 2017. Let us do better for patients like Norman.

Yahya Shehabi, PhD, FANZCA, FCICM, EMBA
Professor, Director Research, Critical Care and PeriOp Medicine
School of Clinical Sciences – Monash Health and Monash University – Melbourne
Professor Intensive Care Medicine – Clinical School of Medicine
University of New South Wales – Sydney
Australia

Reduction of Stress

Nova Acta Leopoldina NF Nr. *421*, 103–106 (2018)

Glucose Utilization and Critical Illness

Steffen Weber-Carstens (Berlin)

Abstract

Hyperglycemia is a common problem in Intensive Care Unit (ICU) patients that increases mortality and the risk of ICU-acquired weakness resulting in poor long-term prognosis. A tight corridor for glucose control is therefore recommended but this currently increases the deleterious risk of hypoglycemic episodes. A tool that continuously monitors blood glucose would help to avoid hyper- and hypoglycemia and improve short- and long-term outcomes, but no sensor has yet been successfully established. This gap has to be systemically closed by industry and clinicians in order to maintain optimum metabolic treatment for our ICU patients.

Zusammenfassung

Hyperglykämie ist ein verbreitetes Problem bei Intensivpatienten, das die Mortalität und die Gefahr der auf der Intensivstation erlangten Schwäche, die schlechte Langzeitprognosen zur Folge hat, erhöht. Ein enger Korridor für eine Blutzuckerkontrolle wird somit empfohlen, aber dies erhöht derzeit das Risiko der hypoglykämischen Vorfälle. Ein Instrument, das kontinuierlich den Blutzucker überwacht, würde helfen, um Hyper- und Hypoglykämie zu vermeiden und Kurz- und Langzeitergebnisse zu verbessern, aber bisher ist kein Sensor erfolgreich hergestellt worden, der in einem breiten Anwendungsfeld eingesetzt werden kann. Diese Lücke muss systematisch durch die Industrie und Klinikärzte geschlossen werden, um eine bestmögliche Stoffwechselbehandlung für unsere Intensivpatienten zu gewährleisten.

Hyperglycemia and metabolic dysregulation are very common in critical illness. They appear to be associated with inflammation and sepsis and cause an increase in mortality (Van den Berghe et al. 2009, Badawi et al. 2012, Weber-Carstens et al. 2013, Marik and Bellomo 2013). Activation of the hypothalamic-pituitary axis causes hyperglycemia through a multitude of mechanisms such as an increased secretion of catabolic hormones, increased hepatic gluconeogenesis and resistance to insulin-mediated uptake of glucose by the skeletal muscle and liver. Furthermore, catecholamine and glucocorticoid therapies are often necessary for the survival of severely ill patients although they add to the problem of hyperglycemia.

It is widely acknowledged that insulin is used to treat hyperglycemic events. The therapeutically targeted range of blood glucose is still under intensive discussion. While trials

The video of presentation is shown online:

in specialized surgical, medical and pediatric intensive care units have shown that a tight corridor for blood glucose levels positively affects outcomes, these results could not be reproduced on a larger multi-center scale (Van den Berghe et al. 2001, 2006, Vlasselaers et al. 2009). When the tight corridor for glucose control was implemented in the daily routines of regular ICUs, the probability of hypoglycemic events increased severely (Finfer et al. 2009). The frequency of these hypoglycemic events might be reduced in the future by continuously monitoring blood glucose levels to give the staff enough time to react to falling blood glucose levels. Until now, no sensor has been successfully established that can be used in a broad field of application. Further research is being conducted on algorithm-based insulin infusion (e.g. LOGIC insulin algorithm), or semi-automated model-based insulin infusion (B. Braun Space Glucose). Evidence also points to a bioenergetic failure of skeletal muscle; the energy supplied through nutrition may not be adequately transported to and metabolized by the muscle during critical illness.

Many trials focus on survival as the main outcome. However, since surviving critical illness has become more and more likely in recent decades, research is starting to shift its focus towards the long-term outcome of critical illness. One deleterious long-term effect of critical illness is Intensive Care Unit Acquired Weakness (ICUAW). This syndrome affects 25 – 100 % of patients in intensive care (Tennilä et al. 2000, Witt et al. 1991, Latronico and Bolton 2011). The most established risk factors are Systemic Inflammatory Response Syndrome (SIRS), sepsis, hyperglycemia and high dose corticosteroid therapy (Van den Berghe et al. 2005, Weber-Carstens et al. 2010, de Jonghe et al. 2009). While continuous neuromuscular blockade and high dose corticosteroid therapy are outdated, the problem of hyperglycemia remains an influenceable risk factor. ICUAW leads to a failure to wean patients from ventilation, restricted mobilization and considerable weakness persisting until the 5-year follow-up (Herridge et al. 2003, 2011). Early physical therapy has been shown to be feasible and beneficial for intensive care patients and may be one future step in preventing ICUAW (Schweickert et al. 2009).

In one retrospective analysis of 74 Acute Respiratory Distress Syndrome (ARDS) survivors, hyperglycemia and high blood glucose variability both predicted a worse cognitive outcome at the 1-year follow-up (Hopkins and Jackson 2006), while another retrospective case-controlled analysis of 37 hypoglycemic incidents revealed an association with poorer visuospatial testing results (Duning et al. 2010). This may be due to several mechanisms. The hippocampus is a region of the brain that is important in coupling short-term and long-term memory. A pilot study showed hypoxic abnormalities in the hippocampus in 5 out of 7 ICU patients who died during delirium and underwent subsequent brain autopsy within 24 hours (Janz et al. 2010). This hypoxic damage may be further aggravated, as hyperglycemia was shown to exacerbate edema in perihematomal regions (Song et al. 2003). Another mechanism may be the increase in reactive oxygen species that cause neuronal cell death as shown after the reperfusion of hypoglycemic cells with glucose (Suh et al. 2007). Interestingly, hyperglycemia could also be correlated with microglial apoptosis as microglial cells play a central role in neuronal function and synaptogenesis, especially in the hippocampus (Polito et al. 2011, Bessis et al. 2007).

References

Badawi, O., Waite, M. D., Fuhrman, S. A., and Zuckerman, I. H.: Association between intensive care unit-acquired dysglycemia and in-hospital mortality. Crit. Care Med. *40*/12, 3180–3188 (2012)

Bessis, A., Béchade, C., Bernard, D., and Roumier, A.: Microglial control of neuronal death and synaptic properties. Glia *55*/3, 233–238 (2007)

Duning, T., van den Heuvel, I., Dickmann, A., Volkert, T., Wempe, C., Reinholz, J., Lohmann, H., Freise, H., and Ellger, B.: Hypoglycemia aggravates critical illness-induced neurocognitive dysfunction. Diabetes Care *33*/3, 639–644 (2010)

Finfer, S., Chittock, D. R., Su, S. Y., Blair, D., Foster, D., Dhingra, V., Bellomo, R., Cook, D., Dodek, P., Henderson, W. R., Hébert, P. C., Heritier, S., Heyland, D. K., McArthur, C., McDonald, E., Mitchell, I., Myburgh, J. A., Norton, R., Potter, J., Robinson, B. G., and Ronco, J. J.: Intensive versus conventional glucose control in critically ill patients. New Engl. J. Med. *360*/13, 1283–1297 (2009)

Herridge, M. S., Cheung, A. M., Tansey, C. M., Matte-Martyn, A., Diaz-Granados, N., Al-Saidi, F., Tansey, C. M., Matte-Martyn, A., Diaz-Granados, N., Al-Saidi, F., Cooper, A. B., Guest, C. B., Mazer, C. D., Mehta, S., Stewart, T. E., Barr, A., Cook, D., Slutsky, A. S., and *Canadian Critical Care Trials Group*: One-year outcomes in survivors of the acute respiratory distress syndrome. New Engl. J. Med. *348*/8, 683–693 (2003)

Herridge, M. S., Tansey, C. M., Matté, A., Tomlinson, G., Diaz-Granados, N., Cooper, A., Guest, C. B., Mazer, C. D., Mehta, S., Stewart, T. E., Kudlow, P., Cook, D., Slutsky, A. S., Cheung, A. M., and *Canadian Critical Care Trials Group*: Functional disability 5 years after acute respiratory distress syndrome. New Engl. J. Med. *364*/14, 1293–1304 (2011)

Hopkins, R. O., and Jackson, J. C.: Long-term neurocognitive function after critical illness. Chest *130*/3, 869–878 (2006)

Janz, D. R., Abel, T. W., Jackson, J. C., Gunther, M. L., Heckers, S., and Ely, E. W.: Brain autopsy findings in intensive care unit patients previously suffering from delirium: A pilot study. J. Crit. Care *25*/3, 538.e7–12 (2010)

Jonghe, B. de, Lacherade, J. C., Sharshar, T., and Outin, H.: Intensive care unit-acquired weakness: Risk factors and prevention. Crit. Care Med. *37*/10, Suppl., S309–315 (2009)

Latronico, N., and Bolton, C. F.: Critical illness polyneuropathy and myopathy: A major cause of muscle weakness and paralysis. Lancet Neurol. *10*/10, 931–941 (2011)

Marik, P. E., and Bellomo, R.: Stress hyperglycemia: An essential survival response! Crit. Care *17*/2, 305 (2013)

Polito, A., Brouland, J. P., Porcher, R., Sonneville, R., Siami, S., Stevens, R. D., Guidoux, C., Maxime, V., de la Grandmaison, G. L., Chrétien, F. C., Gray, F., Annane, D., and Sharshar, T.: Hyperglycaemia and apoptosis of microglial cells in human septic shock. Crit. Care *15*/3, R131 (2011)

Schweickert, W. D., Pohlman, M. C., Pohlman, A. S., Nigos, C., Pawlik, A. J., Esbrook, C. L., Spears, L., Miller, M., Franczyk, M., Deprizio, D., Schmidt, G. A., Bowman, A., Barr, R., McCallister, K. E., Hall, J. B., and Kress, J. P.: Early physical and occupational therapy in mechanically ventilated, critically ill patients: A randomised controlled trial. Lancet *373*/9678, 1874–1882 (2009)

Song, E. C., Chu, K., Jeong, S. W., Jung, K. H., Kim, S. H., Kim, M., and Yoon, B. W.: Hyperglycemia exacerbates brain edema and perihematomal cell death after intracerebral hemorrhage. Stroke *34*/9, 2215–2220 (2003)

Suh, S. W., Gum, E. T., Hamby, A. M., Chan, P. H., and Swanson, R. A.: Hypoglycemic neuronal death is triggered by glucose reperfusion and activation of neuronal NADPH oxidase. J. Clin. Invest. *117*/4, 910–918 (2007)

Tennilä, A., Salmi, T., Pettilä, V., Roine, R. O., Varpula, T., and Takkunen, O.: Early signs of critical illness polyneuropathy in ICU patients with systemic inflammatory response syndrome or sepsis. Intensive Care Med. *26*/9, 1360–1363 (2000)

Van den Berghe, G., Schetz, M., Vlasselaers, D., Hermans, G., Wilmer, A., Bouillon, R., and Mesotten, D.: Clinical review: Intensive insulin therapy in critically ill patients: NICE-SUGAR or leuven blood glucose target? J. Clin. Endocrinol. Metab. *94*/9, 3163–3170 (2009)

Van den Berghe, G., Schoonheydt, K., Becx, P., Bruyninckx, F., and Wouters, P. J.: Insulin therapy protects the central and peripheral nervous system of intensive care patients. Neurology *64*/8, 1348–1353 (2005)

Van den Berghe, G., Wilmer, A., Hermans, G., Meersseman, W., Wouters, P. J., Milants, I., Van Wijngaerden, E., Bobbaers, H., and Bouillon, R.: Intensive insulin therapy in the medical ICU. New Engl. J. Med. *354*/5, 449–461 (2006)

Van den Berghe, G., Wouters, P., Weekers, F., Verwaest, C., Bruyninckx, F., Schetz, M., Vlasselaers, D., Ferdinande, P., Lauwers, P., and Bouillon, R.: Intensive insulin therapy in critically ill patients. New Engl. J. Med. *345*/19, 1359–1367 (2001)

Vlasselaers, D., Milants, I., Desmet, L., Wouters, P. J., Vanhorebeek, I., van den Heuvel, I., Mesotten, D., Casaer, M. P., Meyfroidt, G., Ingels, C., Muller, J., Van Cromphaut, S., Schetz, M., and Van den Ber-

GHE, G.: Intensive insulin therapy for patients in paediatric intensive care: A prospective, randomised controlled study. Lancet *373*/9663, 547–556 (2009)

WEBER-CARSTENS, S., DEJA, M., KOCH, S., SPRANGER, J., BUBSER, F., WERNECKE, K. D., SPIES, C. D., SPULER, S., and KEH, D.: Risk factors in critical illness myopathy during the early course of critical illness: A prospective observational study. Crit. Care *14*/3, R119 (2010)

WEBER-CARSTENS, S., SCHNEIDER, J., WOLLERSHEIM, T., ASSMANN, A., BIERBRAUER, J., MARG, A., AL HASANI, H., CHADT, A., WENZEL, K., KOCH, S., FIELITZ, J., KLEBER, C., FAUST, K., MAI, K., SPIES, C. D., LUFT, F. C., BOSCHMANN, M., SPRANGER, J., and SPULER, S.: Critical illness myopathy and GLUT4: Significance of insulin and muscle contraction. Amer. J. Respir. Crit Care Med. *187*/4, 387–396 (2013)

WITT, N. J., ZOCHODNE, D. W., BOLTON, C. F., GRAND'MAISON, F., WELLS, G., YOUNG, G. B., and SIBBALD, W. J.: Peripheral nerve function in sepsis and multiple organ failure. Chest. *99*/1, 176–184 (1991)

Prof. Dr. med. Steffen WEBER-CARSTENS
Department of Anaesthesiology and
Intensive Care Medicine
Charité Mitte Campus and
Virchow-Klinikum Campus
Charité – Universitätsmedizin Berlin
Augustenburger Platz 1
13353 Berlin
Germany
Tel.: +49 30 450651055
Fax: +49 30 450551909
E-Mail: steffen.weber-carstens@charite.de

Nova Acta Leopoldina NF Nr. *421*, 107–108 (2018)

EEG-Based Diagnostics of Delirium

Arjen Slooter (Utrecht, The Netherlands)

Abstract

Delirium is a major problem in Intensive Care Units (ICU) patients that negatively affects short- and long-term outcomes. Detection of delirium by ICU physicians is poor. An automatic EEG-based delirium monitor seems promising but further research is urgently needed to implement this method into clinical routines. Gaps in implementing promising scientific results in clinical routines have to be minimized by government policies, industry, researchers and clinicians to avoid negative long-term consequences for our ICU patients.

Zusammenfassung

Delirium stellt ein großes Problem bei Intensivpatienten dar, das Kurz- und Langzeitergebnisse negativ beeinflusst. Das Erkennen von Delirium durch Intensivmediziner ist schlecht. Ein automatisches EEG-basiertes Deliriumüberwachungsgerät scheint vielversprechend, aber weitere Forschungsarbeiten sind dringend erforderlich, um diese Methode im Klinikalltag durchzusetzen. Solche Lücken in der Umsetzung zukunftsträchtiger wissenschaftlicher Ergebnisse im Klinikalltag müssen durch die Regierungspolitik, Industrie, Forscher und Klinikärzte auf ein Minimum reduziert werden, um negative Langzeitfolgen für unsere Intensivpatienten zu vermeiden.

1. Introduction

Delirium is common in Intensive Care Unit (ICU) patients and negatively affects outcome. Despite this, ICU physicians struggle to identify delirium in their patients (sensitivity 29 %, van Eijk et al. 2009). Delirium screening tools have been developed to improve detection and, hence, treatment, but these tools are subjective and insensitive in routine, daily practice (van Eijk et al. 2011). We have previously shown that one minute of bipolar electroencephalography (EEG) and the use of relative delta power as an indicator of slowing background activity make it easy to distinguish between patients with and without delirium (van der Kooi et al. 2015).

The video of presentation is shown online:

2. Prototype EEG-Based Delirium Monitor

Based on these findings, a prototype EEG-based delirium monitor was built that had only three electrodes. To validate this EEG-based delirium monitor, we performed a multicentre study on 159 frail, surgical patients. On postoperative days 1 – 3, an EEG test was performed and patients underwent a standardized cognitive assessment that was videotaped. The video was used by two, or when there was no consensus, three delirium experts to diagnose delirium, without taking into account the EEG results. After removing any artefacts, the EEGs were automatically analysed by analysing the relative delta power. Then they were compared with the classifications assigned by the delirium experts. Preliminary findings indicate that routine EEG-based delirium detection is promising. It is objective, quick, easy, and provides a continuous scale, whereas screening is dichotomized. This approach can also be applied with cognitively 'untestable' patients and non-native speakers.

References

van Eijk, M. M., van Marum, R. J., Klijn, I. A., Wit, N. de, Kesecioglu, J., and Slooter, A. J.: Comparison of delirium assessment tools in a mixed intensive care unit. Crit. Care Med *37*/6, 1881–1885 (2009)

van Eijk, M. M., van den Boogaard, M., van Marum, R. J., Benner, P., Eikelenboom, P., Honing, M. L., van der Hoven, B., Horn, J., Izaks, G. J., Kalf, A., Karakus, A., Klijn, I. A., Kuiper, M. A., Leeuw, F. E. de, Man, T. de, van der Mast, R. C., Osse, R. J., Rooij, S. E. de, Spronk, P. E., van der Voort, P. H., van Gool, W. A., and Slooter, A. J.: Routine use of the confusion assessment method for the intensive care unit: a multicenter study. Amer. J. Resp. Crit. Care Med. *184*/3, 340–344 (2011)

van der Kooi, A. W., Zaal, I. J., Klijn, F. A., Koek, H. L., Meijer, R. C., Leijten, F. S., and Slooter, A. J.: Delirium detection using EEG: what and how to measure. Chest *147*/1, 94–101 (2015)

Prof. Arjen Slooter, MD, PhD
Professor of Intensive Care Neuropsychiatry
Brain Center Rudolf Magnus
Utrecht University
Consultant Neurologist – Intensivist
Department of Intensive Care Medicine
University Medical Center Utrecht
Postbus 85500
3508 GA Utrecht
The Netherlands
Tel.: +31 88 7555555
Fax: +31 88 7555032
E-Mail: A.Slooter-3@umcutrecht.nl

Nova Acta Leopoldina NF Nr. *421*, 109–114 (2018)

$GABA_A$ Receptors: The Forgotten Target

Hanns Ulrich Zeilhofer (Zurich, Switzerland)

Abstract

There is a wide spectrum of $GABA_A$ receptors that could lead to the development of better-tolerated benzodiazepines and new indications for their application, like depression, schizophrenia, autism, cognitive enhancement, and chronic pain. Preclinical experiments show promising results. The challenge is to translate basic science findings into clinical application, possibly improving short- and long-term outcomes.

Zusammenfassung

Es gibt ein breites Spektrum an $GABA_A$-Rezeptoren, die zur Entwicklung von besser verträglichen Benzodiazepinen und neuen Indikationen für ihre Anwendung, wie Depressionen, Schizophrenie, Autismus, kognitive Verbesserung und chronische Schmerzen, führen könnten. Präklinische Experimente zeigen vielversprechende Ergebnisse. Die Aufgabe besteht darin, Erkenntnisse der Grundlagenwissenschaft in neue therapeutische Ansätze zu übertragen, die möglicherweise Kurz- und Langzeitergebnisse verbessern.

γ-aminobutyric acid (GABA) is the major inhibitory neurotransmitter in the mammalian central nervous system (CNS). It acts by activating chloride-permeable ion channels ($GABA_A$ receptors), which hyperpolarize neurons and $GABA_B$ receptors coupled to G-proteins, which activate potassium channels and inhibit presynaptic Ca^{2+} channels. GABA-releasing (GABAergic) neurons and GABA receptors are found throughout almost all parts of the CNS including the spinal cord. $GABA_A$ receptors are the targets of a variety of modulators including endogenous neurosteroids, ethanol and several classes of widely used drugs. Most of these act as positive allosteric modulators, enhancing the action of GABA at its receptors. Drugs that target $GABA_A$ receptors include the widely used benzodiazepines (including the so-called Z drugs zolpidem and zopiclone) and barbiturates whose use is meanwhile restricted to intravenous anesthesia and to the treatment of epilepsy. Indications for benzodiazepines are primarily sleep and anxiety disorders and epilepsy. Given the almost ubiquitous presence of GABA and $GABA_A$ receptors in the mammalian CNS, the list of indications is surprisingly short. This can partially be attributed to the side effects of benzodiazepine site ligands ob-

The video of presentation is shown online:

served during chronic treatment. Fears about addiction and physical dependence have led to significant decreases in their use, and, depending on the indication, sedation, impaired motor coordination and muscle relaxation are well-known side effects. More recently, additional concerns have been raised such as a potential increase in the risk of dementia after prolonged use and neurotoxic effects when used as an anesthetic in children under the age of four. These side effects have led scientists to re-examine hitherto unexploited opportunities for the development of better-tolerated benzodiazepines.

$GABA_A$ receptors are heteropentameric anion channels in the cys-loop family built from a repertoire of nineteen subunits encoded by separate genes that would, in principle and solely based on combinatorial considerations, allow the formation of more than a million different subtypes (Fig. 1). This number is drastically reduced when considerations are restricted to the benzodiazepine-sensitive $GABA_A$ receptors, which make up the vast majority of all $GABA_A$ receptors in the CNS (Olsen and Sieghart 2008). Benzodiazepine-sensitive receptors contain α, β and a γ subunit in a 2:2:1 stoichiometry. The binding site of classical benzodiazepines in the $GABA_A$ receptor complex is formed by an interface between one α subunit and the γ subunit, whereby the α subunit must be α1, α2, α3 or α5 and the γ subunit be γ2, which also mediates the clustering of brain $GABA_A$ receptors at postsynaptic sites. This basically reduces the number of $GABA_A$ receptor subtypes sensitive to classical benzodiazepines to four.

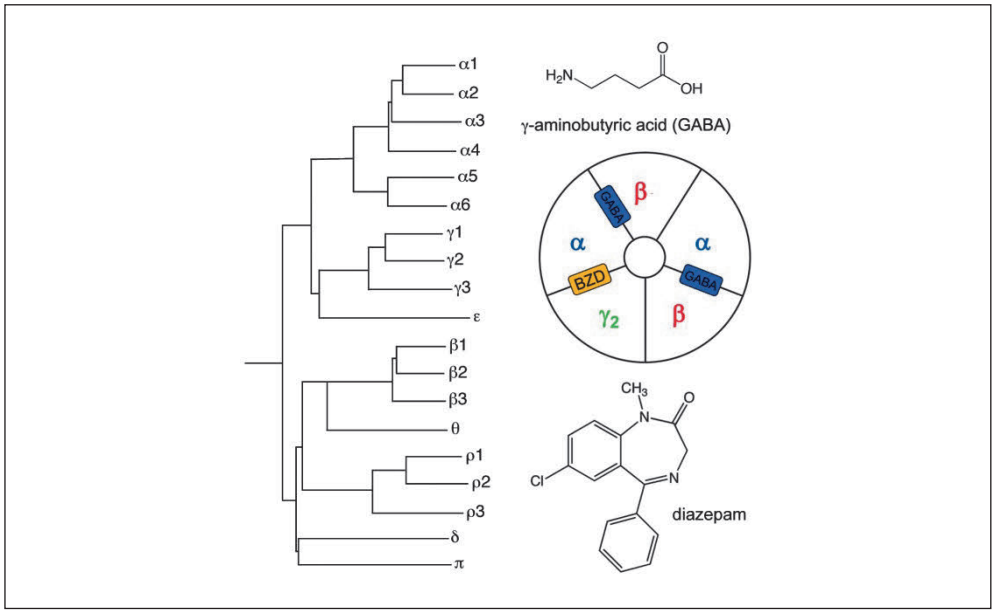

Fig. 1 Dendrogram of $GABA_A$ receptor subunits, structure of GABA, wheel arrangement of benzodiazepine-sensitive $GABA_A$ receptors, and structure of the classical benzodiazepines site agonist diazepam (adapted from Barnard et al. 1998).

The most abundant $GABA_A$ receptor isoform is composed of α1/β2/γ2 subunits (more than 60 % of all $GABA_A$ receptors) while α2, α3 or α5 containing $GABA_A$ receptors contribute to

5 – 20 % of all $GABA_A$ receptors in the CNS (Benke et al. 2004). Nevertheless, α2, α3, or α5 $GABA_A$ receptors can be the dominant subtypes in particular areas of the CNS or in certain subcellular domains. Examples of such areas and domains include the high-density expression of α2 in the amygdala or of α2 and α5 subunits in the hippocampus, or of α2 in the axon initial segment of hippocampal and cortical pyramidal neurons. Much effort has been spent in the last 15 years to attribute specific physiological functions of $GABA_A$ receptors or pharmacological actions of benzodiazepine site ligands to defined subtypes of $GABA_A$ receptors.

A highly versatile approach to this problem has been the generation of point mutated mice, so called knock-in mice, in which a histidine to alanine (H → R) amino acid exchange has been separately introduced into each of the α subunits to abrogate the diazepam binding site (Rudolph and Mohler 2004).

Importantly, these receptors still respond normally to the endogenous agonist GABA but are no longer potentiated by diazepam and most other benzodiazepine site ligands. Using these mice has made it possible to attribute several benzodiazepine effects to defined $GABA_A$ receptor subtypes. Most importantly, it has been demonstrated that the sedative and anticonvulsive actions are mediated by $GABA_A$ receptors containing the α1 subunit (α1$GABA_A$ receptors) (Rudolph et al. 1999), while anxiolysis is mediated by α2$GABA_A$ receptors (Löw et al. 2000). The muscle relaxant effects of benzodiazepines occur *via* the α2$GABA_A$ and α3$GABA_A$ receptors (Crestani et al. 2001), and impairment of motor coordination, which underlies the tendency of elderly patients on benzodiazepine to fall, is mediated by the α3$GABA_A$ and possibly α1$GABA_A$ receptors (Rudolph et al. 1999, Löw et al. 2000, Ralvenius et al. 2015). Many other unwanted effects, such as reward/addiction (Tan et al. 2010) and amnesia (Rudolph et al. 1999) have also been attributed to α1$GABA_A$ receptors. Tolerance development, which is a loss of drug effect during prolonged treatment, is also reduced in certain $GABA_A$ receptor H → R point mutated mice, but the relevant subtype is different for different pharmacological actions (Ralvenius et al. 2015, Knabl et al. 2008, van Rijnsoever et al. 2004). These results strongly suggest that subtype selective benzodiazepine site agonists, in particular compounds lacking activity at the α1$GABA_A$ receptors, should be better-tolerated benzodiazepines.

Tab. 1 Contribution of $GABA_A$ receptor subtypes to pharmacological effects of benzodiazepines

	$GABA_A$ Receptor Subtype			
	α1	α2	α3	α5
Sedation	✓			
Anxiolysis		✓	(✓)	
Amnesia	✓			
Motor impairment	(✓)		✓	
Muscle relaxation		✓	✓	
Addiction/reward	✓			
Cognitive impairment				✓
Anticonvulsion	✓			
Antihyperalgesia		✓		

Subsequent work with these $GABA_A$ receptor point mutated mice has also revealed new pharmacological effects and new potential indications. Experiments in α1(H→R)$GABA_A$ receptor point mutated mice were instrumental in this endeavor as the use of these mice allowed benzodiazepine effects to be investigated in the absence of confounding or dose-limiting sedation. Such experiments revealed that the targeting of non-α1$GABA_A$ receptors in point mutated mice or with α1-sparing benzodiazepine site ligands should not only alleviate anxiety in the absence of sedation, but should also have a therapeutic potential in diseases which have hitherto not been considered indications for benzodiazepines. Potentiation of $GABA_A$ receptors in the dorsal horn, the sensory part of the spinal cord, evokes profound antihyperalgesia in mouse models of chronic inflammatory and neuropathic pain, mainly *via* the α2$GABA_A$ receptors (Ralvenius et al. 2015, Knabl et al. 2008, 2009, Witschi et al. 2011). Other potentially new indications include depression, schizophrenia, and autism spectrum disorders, in which impaired GABAergic inhibition appears to be an important contributor (Rudolph and Mohler 2014). Another important development relates to the field of cognitive enhancement. Inverse agonists at the α5$GABA_A$ receptors, i.e. compounds that reduce the inhibitory effect of GABA at the α5$GABA_A$ receptors, are currently in clinical trials, testing their potential as drugs that would improve cognitive function in Down syndrome patients (Rudolph and Mohler 2014).

Motivated by the results from preclinical experiments performed on point mutated mice, several pharmaceutical companies have developed benzodiazepine site ligands with improved subtype-specificity. A significant number of compounds with reduced activity at the α1$GABA_A$ receptors have been developed by both large pharmaceutical companies, such as Merck or Astra-Zeneca, and biotech companies, such as Neurosearch. Many of these compounds exhibited the desired reduction in activity at the α1$GABA_A$ receptors (TPA023 [Atack et al. 2006], NS11394 [Munro et al. 2008], HZ-166 [Rivas et al. 2009]). Some even showed absolutely no activity at the α1$GABA_A$ receptors (L-838417 [McKernan et al. 2000], TPA023B [Atack et al. 2011]) with retained partial agonistic activity at the α2, α3, and α5 $GABA_A$ receptors. Most of these drug development programs focused, at least initially, on the non-sedative anxiolytics, but other indications, such as chronic pain, have also been addressed both by pharmaceutical companies and groups in academia. Many of these compounds exhibited anxiolytic and antihyperalgesic properties in the absence of sedation – at least in preclinical models (for a review see Zeilhofer et al. 2012). Despite these encouraging results from preclinical studies, none of the subtype selective compounds has so far been approved for use in humans. The reasons for this have only partially been disclosed. Publicly available information includes unfavorable pharmacokinetics and compounds rather than class-related toxicity.

Although no subtype-selective benzodiazepines have so far been approved for use in humans, preclinical data is strongly encouraging, and several drug development programs are ongoing in both academia and industry. Future programs may also address subtypes of $GABA_A$ receptors and binding sites not discussed above. Such hitherto unexploited opportunities may include approaches that are based on the diversity of β or γ subunits.

References

Atack, J. R., Wafford, K. A., Tye, S. J., Cook, S. M., Sohal, B., Pike, A., Sur, C., Melillo, D., Bristow, L., Bromidge, F., Ragan, I., Kerby, J., Street, L., Carling, R., Castro, J. L., Whiting, P., Dawson, G. R., and McKernan, R. M.: TPA023 [7-(1,1-dimethylethyl)-6-(2-ethyl-2H-1,2,4-triazol-3-ylmethoxy)-3-(2-fluorophenyl)-1,2,4-triazolo[4,3-b]pyridazine], an agonist selective for α2- and α3-containing $GABA_A$ receptors, is a nonsedating anxiolytic in rodents and primates. J. Pharmacol. Exp. Ther. *316*, 410–422 (2006)

Atack, J. R., Hallett, D. J., Tye, S., Wafford, K. A., Ryan, C., Sanabria-Bohórquez, S. M., Eng, W. S., Gibson, R. E., Burns, H. D., Dawson, G. R., Carling, R. W., Street, L. J., Pike, A., Lepeleire, I. de, Van Laere, K., Bormans, G., Hoon, J. N. de, Van Hecken, A., McKernan, R. M., Murphy, M. G., and Hargreaves, R. J.: Preclinical and clinical pharmacology of TPA023B, a $GABA_A$ receptor α2/α3 subtype-selective partial agonist. J. Psychopharmacol. *25*, 329–344 (2011)

Barnard, E. A., Skolnick, P., Olsen, R. W., Mohler, H., Sieghart, W., Biggio, G., Braestrup, C., Bateson, A. N., and Langer, S. Z.: International Union of Pharmacology. XV. Subtypes of γ-aminobutyric acidA receptors: Classification on the basis of subunit structure and receptor function. Pharmacol. Rev. *50*, 291–313 (1998)

Benke, D., Fakitsas, P., Roggenmoser, C., Michel, C., Rudolph, U., and Mohler, H.: Analysis of the presence and abundance of $GABA_A$ receptors containing two different types of α subunits in murine brain using point-mutated α subunits. J. Biol. Chem. *279*, 43654–43660 (2004)

Crestani, F., Löw, K., Keist, R., Mandelli, M., Möhler, H., and Rudolph, U.: Molecular targets for the myorelaxant action of diazepam. Mol. Pharmacol. *59*, 442–445 (2001)

Knabl, J., Witschi, R., Hösl, K., Reinold, H., Zeilhofer, U. B., Ahmadi, S., Brockhaus, J., Sergejeva, M., Hess, A., Brune, K., Fritschy, J. M., Rudolph, U., Möhler, H., and Zeilhofer, H. U.: Reversal of pathological pain through specific spinal $GABA_A$ receptor subtypes. Nature *451*, 330–334 (2008)

Knabl, J., Zeilhofer, U. B., Crestani, F., Rudolph, U., and Zeilhofer, H. U.: Genuine antihyperalgesia by systemic diazepam revealed by experiments in $GABA_A$ receptor point-mutated mice. Pain *141*, 233–238 (2009)

Löw, K., Crestani, F., Keist, R., Benke, D., Brünig, I., Benson, J. A., Fritschy, J. M., Rülicke, T., Bluethmann, H., Möhler, H., and Rudolph, U.: Molecular and neuronal substrate for the selective attenuation of anxiety. Science *290*, 131–134 (2000)

McKernan, R. M., Rosahl, T. W., Reynolds, D. S., Sur, C., Wafford, K. A., Atack, J. R., Farrar, S., Myers, J., Cook, G., Ferris, P., Garrett, L., Bristow, L., Marshall, G., Macaulay, A., Brown, N., Howell, O., Moore, K. W., Carling, R. W., Street, L. J., Castro, J. L., Ragan, C. I., Dawson, G. R., and Whiting, P. J.: Sedative but not anxiolytic properties of benzodiazepines are mediated by the $GABA_A$ receptor α1 subtype. Nature Neurosci. *3*, 587–592 (2000)

Munro, G., Lopez-Garcia, J. A., Rivera-Arconada, I., Erichsen, H. K., Nielsen, E. Ø., Larsen, J. S., Ahring, P. K., and Mirza, N. R.: Comparison of the novel subtype-selective $GABA_A$ receptor-positive allosteric modulator NS11394 [3'-[5-(1-hydroxy-1-methyl-ethyl)-benzoimidazol-1-yl]-biphenyl-2-carbonitrile] with diazepam, zolpidem, bretazenil, and gaboxadol in rat models of inflammatory and neuropathic pain. J. Pharmacol. Exp. Ther. *327*, 969–981 (2008)

Olsen, R. W., and Sieghart, W.: International Union of Pharmacology. LXX. Subtypes of γ-aminobutyric $acid_A$ receptors: classification on the basis of subunit composition, pharmacology, and function. Update. Pharmacol. Rev. *60*, 243–260 (2008)

Ralvenius, W. T., Benke, D., Acuña, M. A., Rudolph, U., and Zeilhofer, H. U.: Analgesia and unwanted benzodiazepine effects in point-mutated mice expressing only one benzodiazepine-sensitive $GABA_A$ receptor subtype. Nature Commun. *6*, 6803 (2015)

Rivas, F. M., Stables, J. P., Murphree, L., Edwankar, R. V., Edwankar, C. R., Huang, S., Jain, H. D., Zhou, H., Majumder, S., Sankar, S., Roth, B. L., Ramerstorfer, J., Furtmüller, R., Sieghart, W., and Cook, J. M.: Antiseizure activity of novel γ-aminobutyric $acid_A$ receptor subtype-selective benzodiazepine analogues in mice and rat models. J. Med. Chem. *52*, 1795–1798 (2009)

Rudolph, U., Crestani, F., Benke, D., Brünig, I., Benson, J. A., Fritschy, J. M., Martin, J. R., Bluethmann, H., and Möhler, H.: Benzodiazepine actions mediated by specific γ-aminobutyric $acid_A$ receptor subtypes. Nature *401*, 796–800 (1999)

Rudolph, U., and Mohler, H.: Analysis of $GABA_A$ receptor function and dissection of the pharmacology of benzodiazepines and general anesthetics through mouse genetics. Annu. Rev. Pharmacol. Toxicol. *44*, 475–498 (2004)

Rudolph, U., and Mohler, H.: $GABA_A$ receptor subtypes: Therapeutic potential in Down syndrome, affective disorders, schizophrenia, and autism. Annu. Rev. Pharmacol. Toxicol. *54*, 483–507 (2014)

Tan, K. R., Brown, M., Labouèbe, G., Yvon, C., Creton, C., Fritschy, J. M., Rudolph, U., and Lüscher C.: Neural bases for addictive properties of benzodiazepines. Nature *463*, 769–774 (2010)

van Rijnsoever, C., Täuber, M., Choulli, M. K., Keist, R., Rudolph, U., Mohler, H., Fritschy, J. M., and Crestani, F.: Requirement of α5-$GABA_A$ receptors for the development of tolerance to the sedative action of diazepam in mice. J. Neurosci. *24*, 6785–6790 (2004)

Witschi, R., Punnakkal, P., Paul, J., Walczak, J. S., Cervero, F., Fritschy, J. M., Kuner, R., Keist, R., Rudolph, U., and Zeilhofer, H. U.: Presynaptic α2-$GABA_A$ receptors in primary afferent depolarization and spinal pain control. J. Neurosci. *31*, 8134–8142 (2011)

Zeilhofer, H. U., Benke, D., and Yevenes, G. E.: Chronic pain states: pharmacological strategies to restore diminished inhibitory spinal pain control. Annu. Rev. Pharmacol. Toxicol. *52*, 111–133 (2012)

Prof. Dr. Hanns Ulrich Zeilhofer
Institute of Pharmacology and Toxicology
University of Zurich
Winterthurerstrasse 190
CH-8057 Zurich
Switzerland
Tel.: +41 44 6355912
Fax: +41 44 6355888
E-Mail: zeilhofer@pharma.uzh.ch

Nova Acta Leopoldina NF Nr. *421*, 115–119 (2018)

Reducing Stress, Increasing Strength: Early Mobilization and Impact on Long-Term Outcome

Nicholas Hart (London, UK)

Abstract

Intensive Care Unit (ICU) survivors exhibit skeletal muscle wasting, weakness, loss of physical activity and functional impairment. Severity of critical illness determines the extent of skeletal muscle wasting with age, chronic disease and ICU stay length determine functional outcome. Early mobilization during critical illness could play a role in enhancing long-term functional outcome but more work focused on the patients most likely to benefit is required.

Zusammenfassung

Überlebende von Intensivbehandlungen zeigen Skelettmuskelverfall, Schwäche, Verlust an physischer Aktivität und funktionale Beeinträchtigungen. Die Schwere der kritischen Erkrankung bestimmt das Ausmaß des Skelettmuskelverfalls mit dem Alter, die chronische Erkrankung und die Länge des Intensivstationsaufenthaltes determiniert das funktionelle Ergebnis. Frühe Mobilisierung während der schweren Erkrankung kann eine Rolle in der Verbesserung der Langzeitfunktionsresultate spielen, aber weitere Arbeit, die sich auf Patienten, die am wahrscheinlichsten davon profitieren, fokussiert, muss noch geleistet werden.

Intensive Care Unit (ICU) survivors exhibit skeletal muscle wasting, weakness, loss of physical activity and functional impairment. Seminal work by de Jonghe et al. in 2002 and Herridge et al. in 2003 that reported the incidence of ICU-acquired weakness (ICUAW) and outcome following critical illness was a major catalyst for the last 15 years of work in this emerging clinical field. With a variable prevalence rate from 25 % to 50 %, ICUAW is associated with the severity of critical illness as evidenced by the relationship with sepsis and multi organ failure (Weber-Carstens et al. 2010). Importantly, ongoing systemic inflammation following the resolution of critical illness has been shown to be associated with persistent ICUAW (Griffith et al. 2016). Skeletal muscle wasting and weakness are observed in the diaphragm and peripheral skeletal muscle resulting in both delayed weaning from mechanical ventilation and functional disability. Both wasting and weakness occur early and rapidly and can be pronounced. If peripheral muscle weakness is present, diaphragm weakness is more likely with diaphragm and peripheral muscle weakness predicting clinical outcome (de Jong-

The video of presentation is shown online:

HE et al. 2002, WATSON et al. 2001, GOLIGHER et al. 2015, HUSSAIN et al. 2016, LEVINE et al. 2008, JABER et al. 2011, MCNELLY et al. 2016, PUTHUCHEARY et al. 2013, 2017, CONNOLLY et al. 2013, 2015, ALI et al. 2008). These data strongly support the clinical paradigm of muscle structure to function to clinical outcome (Fig. 1).

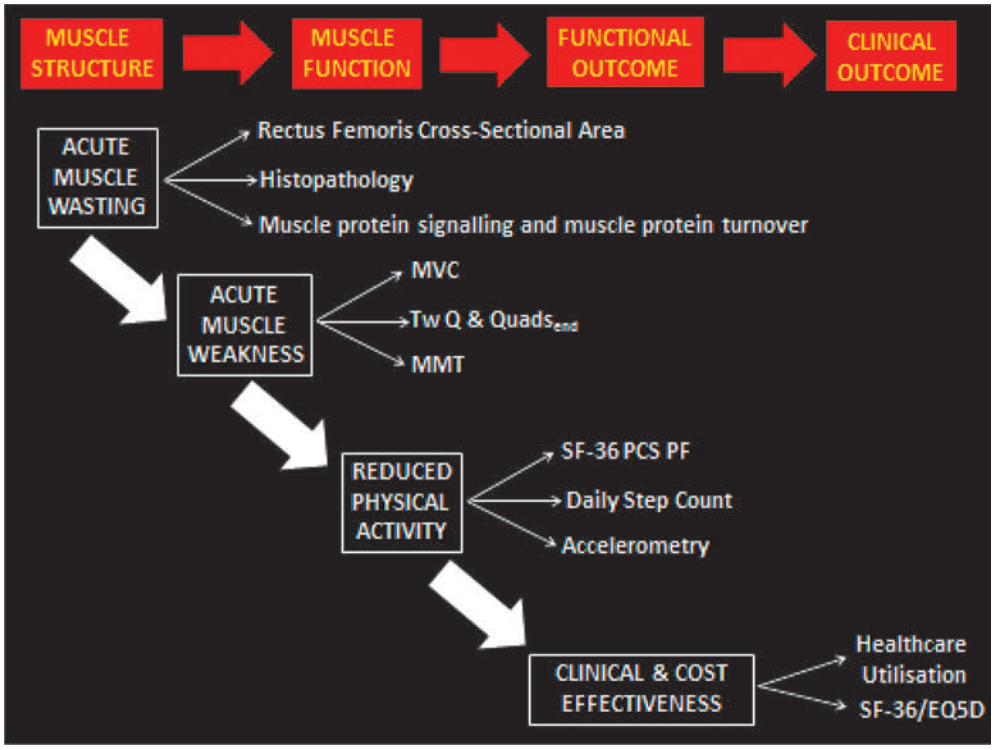

Fig. 1 Skeletal muscle structure to function to clinical outcome

Early mobilization to prevent, or ameliorate, ICUAW and enhance functional outcome is a hot clinical research topic. Indeed, a *Pubmed* search for 'early mobilisation and intensive care unit' shows 402 papers published between 1976 and 2017. Interestingly, 59 % of these manuscripts have been published in the last five years. The landmark randomized clinical trial from SCHWEICKERT et al. in 2009 demonstrated that daily interruption of sedation with early physical therapy in combination with occupational therapy, in medical ICU patients, improves functional independent status at hospital discharge (SCHWEICKERT et al. 2009). In 2016, SCHALLER et al. demonstrated that early goal-directed mobilization in surgical ICU patients enhanced mobilization. Despite these promising data, MOSS et al. (2016) failed to demonstrate that intensive physical therapy in the ICU, on the ward post ICU discharge and in the outpatients or at home after hospital discharge an improvement in physical functional performance at 4 weeks. These data are further supported by randomized clinical trial data from MORRIS et al. (2016) who failed to demonstrate a reduction in hospital stay length when rehabilitation therapy, including resistance exercises, was delivered daily three times to med-

ical ICU patients. The barriers and enablers that influence early mobilization, rehabilitation physical activity in ICU survivors must be considered (Parry et al. 2017).

Detailed evaluation of these clinical trial data are important to determine the reason for responders and non-responders. If we are effectively delivering treatment over and above the control population, then it is essential to define the target patient population most likely to benefit. In particular, we must consider the pre-morbid ICU condition. Recent data from Herridge et al. (2016, Parry et al. 2017) demonstrated that age and ICU length of stay are important factors determining functional outcome, which is supported by the data from McNelly et al. (2016) who also demonstrated that presence of chronic disease was associated with reduced physical activity six months post ICU discharge. Finally, a core outcome set, post critical illness needs to be developed which includes validated, reliable and feasible measures to ensure that the therapeutic strategies and patent centered outcomes comparable (Needham n. d.).

Translational skeletal muscle science is essential to design future clinical trials to assess and treat skeletal muscle wasting during critical illness and post critical illness. Severity of critical illness determines the extent of skeletal muscle wasting with age, chronic disease and ICU length of stay determine functional outcome. Early mobilization during critical illness could have a role in enhancing long-term functional outcome but more work focused on the patients most likely to benefit is required. Indeed, enrichment of the target population with a focus on the pre-ICU condition is necessary. The development of physical, psychological, cognitive and social long-term outcome measures is a priority.

References

Ali, N. A., O'Brien, J. M. Jr., Hoffmann, S. P., Phillips, G., Garland, A., Finley, J. C., Almoosa, K., Hejal, R., Wolf, K. M., Lemeshow, S., Connors, A. F. Jr., Marsh, C. B., and *Midwest Critical Care Consortium*: Acquired weakness, handgrip strength, and mortality in critically ill patients. Amer. J. Respir Crit. Care Med. *178*, 261–268 (2008)

Connolly, B. A., Jones, G. D., Curtis, A. A., Murphy, P. B., Douiri, A., Hopkinson, N. S., Polkey, M. I., Moxham, J., and Hart, N.: Clinical predictive value of manual muscle strength testing during critical illness: an observational cohort study. Crit. Care *17*, R229 (2013)

Connolly, B. A., MacBean, V., Crowley, C., Lunt, A., Moxham, J., Rafferty, G. F., and Hart, N.: Ultrasound for the assessment of peripheral skeletal muscle architecture in critical illness: a systematic review. Crit. Care Med. *43*, 897–905 (2015)

Goligher, E. C., Fan, E., Herridge, M. S., Murray, A., Vorona, S., Brace, D., Rittayamai, N., Lanys, A., Tomlinson, G., Singh, J. M., Bolz, S. S., Rubenfeld, G. D., Kavanagh, B. P., Brochard, L. J., and Ferguson, N. D.: Evolution of diaphragm thickness during mechanical ventilation. Impact of inspiratory effort. Amer. J. Respir Crit. Care Med. *192*, 1080–1088 (2015)

Griffith, D. M., Lewis, S., Rossi, A. G., Rennie, J., Salisbury, L., Merriweather, J. L., Templeton, K., Walsh, T. S., and *RECOVER Investigators*: Systemic inflammation after critical illness: relationship with physical recovery and exploration of potential mechanisms. Thorax *71*/9, 820–829 (2016)

Herridge, M. S., Cheung, A. M., Tansey, C. M., Matte-Martyn, A., Diaz-Granados, N., Al-Saidi, F., Cooper, A. B., Guest, C. B., Mazer, C. D., Mehta, S., Stewart, T. E., Barr, A., Cook, D., Slutsky, A. S., and *Canadian Critical Care Trials Group*: One-year outcomes in survivors of the acute respiratory distress syndrome. New Engl. J. Med. *348*/8, 683–693 (2003)

Herridge, M. S., Chu, L. M., Matte, A., Tomlinson, G., Chan, L., Thomas, C., Friedrich, J. O., Mehta, S., Lamontagne, F., Levasseur, M., Ferguson, N. D., Adhikari, N. K., Rudkowski, J. C., Meggison, H., Skrobik, Y., Flannery, J., Bayley, M., Batt, J., Santos, C. D., Abbey, S. E., Tan, A., Lo, V., Mathur, S., Parotto, M., Morris, D., Flockhart, L., Fan, E., Lee, C. M., Wilcox, M. E., Ayas, N., Choong, K., Fowler, R., Scales, D. C., Sinuff, T., Cuthbertson, B. H., Rose, L., Robles, P., Burns, S., Cypel, M., Singer,

L., Chaparro, C., Chow, C. W., Keshavjee, S., Brochard, L., Hebert, P., Slutsky, A. S., Marshall, J. C., Cook, D., Cameron, J. I., *RECOVER Program Investigators* and *Canadian Critical Care Trials Group*: The RECOVER Program: Disability risk groups and 1-year outcome after 7 or more days of mechanical ventilation. Amer. J. Respir Crit. Care Med. *194*/7, 831–844 (2016)

Hussain, S. N., Cornachione, A. S., Guichon, C., Al Khunaizi, A., Leite Fde, S., Petrof, B. J., Mofarrahi, M., Moroz, N., Varennes, B. de, Goldberg, P., and Rassier, D. E.: Prolonged controlled mechanical ventilation in humans triggers myofibrillar contractile dysfunction and myofilament protein loss in the diaphragm. Thorax *71*, 436–445 (2016)

Jaber, S., Petrof, B. J., Jung, B., Chanques, G., Berthet, J. P., Rabuel, C., Bouyabrine, H., Courouble, P., Koechlin-Ramonatxo, C., Sebbane, M., Similowski, T., Scheuermann, V., Mebazaa, A., Capdevila, X., Mornet, D., Mercier, J., Lacampagne, A., Philips, A., and Matecki, S.: Rapidly progressive diaphragmatic weakness and injury during mechanical ventilation in humans. Amer. J. Respir Crit. Care Med. *183*, 364–371 (2011)

Jonghe, B. de, Sharshar, T., Lefaucheur, J. P., Authier, F. J., Durand-Zaleski, I., Boussarsar, M., Cerf, C., Renaud, E., Mesrati, F., Carlet, J., Raphaël, J. C., Outin, H., Bastuji-Garin, S., and *Groupe de Réflexion et d'Etude des Neuromyopathies en Réanimation*: Paresis acquired in the intensive care unit: a prospective multicenter study. JAMA *288*/22, 2859–2867 (2002)

Levine, S., Nguyen, T., Taylor, N., Friscia, M. E., Budak, M. T., Rothenberg, P., Zhu, J., Sachdeva, R., Sonnad, S., Kaiser, L. R., Rubinstein, N. A., Powers, S. K., and Shrager, J. B.: Rapid disuse atrophy of diaphragm fibers in mechanically ventilated humans. New Engl. J. Med. *358*, 1327–1335 (2008)

McNelly, A. S., Rawal, J., Shrikrishna, D., Hopkinson, N. S., Moxham, J., Harridge, S. D., Hart, N., Montgomery, H. E., and Puthucheary, Z. A.: An exploratory study of long-term outcome measures in critical illness survivors: Construct validity of physical activity, frailty, and health-related quality of life measures. Crit. Care Med. *44*, e362–369 (2016)

Morris, P. E., Berry, M. J., Files, D. C., Thompson, J. C., Hauser, J., Flores, L., Dhar, S., Chmelo, E., Lovato, J., Case, L. D., Bakhru, R. N., Sarwal, A., Parry, S. M., Campbell, P., Mote, A., Winkelman, C., Hite, R. D., Nicklas, B., Chatterjee, A., and Young, M. P.: Standardized rehabilitation and hospital length of stay among patients with acute respiratory failure: A randomized clinical trial. JAMA *315*, 2694–2702 (2016)

Moss, M., Nordon-Craft, A., Malone, D., Van Pelt, D., Frankel, S. K., Warner, M. L., Kriekels, W., McNulty, M., Fairclough, D. L., and Schenkman, M.: A randomized trial of an intensive physical therapy program for patients with acute respiratory failure. Amer. J. Respir Crit. Care Med. *193*/10, 1101–1110 (2016)

Needham, D.: Improving Long-Term Outcomes Research for Acute Respiratory Failure. (n. d.) http://www.improvelto.com/

Parry, S. M., Knight, L. D., Connolly, B., Baldwin, C., Puthucheary, Z., Morris, P., Mortimore, J., Hart, N., Denehy, L., and Granger, C. L.: Factors influencing physical activity and rehabilitation in survivors of critical illness: a systematic review of quantitative and qualitative studies. Intensive Care Med. *43*/4, 531–542 (2017)

Puthucheary, Z. A., McNelly, A. S., Rawal, J., Connolly, B., Sidhu, P. S., Rowlerson, A., Moxham, J., Harridge, S. D., Hart, N., and Montgomery, H. E.: Rectus femoris cross-sectional area and muscle layer thickness: Comparative markers of muscle wasting and weakness. Amer. J. Respir Crit. Care Med. *195*, 136–138 (2017)

Puthucheary, Z. A., Rawal, J., McPhail, M., Connolly, B., Ratnayake, G., Chan, P., Hopkinson, N. S., Phadke, R., Dew, T., Sidhu, P. S., Velloso, C., Seymour, J., Agley, C. C., Selby, A., Limb, M., Edwards, L. M., Smith, K., Rowlerson, A., Rennie, M. J., Moxham, J., Harridge, S. D., Hart, N., and Montgomery, H. E.: Acute skeletal muscle wasting in critical illness. JAMA *310*, 1591–1600 (2013)

Schaller, S. J., Anstey, M., Blobner, M., Edrich, T., Grabitz, S. D., Gradwohl-Matis, I., Heim, M., Houle, T., Kurth, T., Latronico, N., Lee, J., Meyer, M. J., Peponis, T., Talmor, D., Velmahos, G. C., Waak, K., Walz, J. M., Zafonte, R., and Eikermann, M., and *International Early SOMS-guided Mobilization Research Initiative*: Early, goal-directed mobilisation in the surgical intensive care unit: a randomised controlled trial. Lancet *388*/10052, 1377–1388 (2016)

Schweickert, W. D., Pohlman, M. C., Pohlman, A. S., Nigos, C., Pawlik, A. J., Esbrook, C. L., Spears, L., Miller, M., Franczyk, M., Deprizio, D., Schmidt, G. A., Bowman, A., Barr, R., McCallister, K. E., Hall, J. B., and Kress, J. P.: Early physical and occupational therapy in mechanically ventilated, critically ill patients: a randomised controlled trial. Lancet *373*/9678, 1874–1882 (2009)

Watson, A. C., Hughes, P. D., Louise Harris, M., Hart, N., Ware, R. J., Wendon, J., Green, M., and Moxham, J.: Measurement of twitch transdiaphragmatic, esophageal, and endotracheal tube pressure with bilateral anterolateral magnetic phrenic nerve stimulation in patients in the intensive care unit. Crit. Care Med. *29*, 1325–1331 (2001)

Weber-Carstens, S., Deja, M., Koch, S., Spranger, J., Bubser, F., Wernecke, K. D., Spies, C. D., Spuler, S., and Keh, D.: Risk factors in critical illness myopathy during the early course of critical illness: a prospective observational study. Crit. Care *14*/3, R119 (2010)

Prof. Dr. Nicholas Hart

Clinical Director of Lane Fox Respiratory Service
St Thomas' Hospital United Kingdom

Professor of Respiratory and Critical Care Medicine
School of Basic and Biomedical Sciences
Kings College London

Director of Research Delivery
Guy's and St Thomas' NHS Foundation Trust
Westminster Bridge Road

London SE1 7EH
United Kingdom
Tel.: +44 20 71886115
E-Mail: Nicholas.Hart@gstt.nhs.uk

Surviving the Intensive Care Unit

Nova Acta Leopoldina NF Nr. *421*, 123 –126 (2018)

Surgery Successful – But Patient Demented

Georg Winterer (Berlin)

Abstract

Postoperative delirium (POD) and postoperative cognitive dysfunction (POCD) are becoming increasingly prevalent and constitute a major problem. They are associated with longer and more costly hospital treatment as well as increased mortality. A lack of understanding about the relevant pathomechanisms leads to an urgent medical need for effective diagnostic tools and treatments. The EU-funded research project BioCog therefore aims to develop a diagnostic tool for clinical practice that predicts POD and POCD. This project will hopefully close a major gap between evidence and patient-centered outcomes.

Zusammenfassung

Postoperatives Delirium (POD) und postoperative kognitive Dysfunktion (POCD) sind zunehmend verbreitet und stellen ein großes Problem dar. Sie werden mit einer längeren und kostspieligeren Krankenhausbehandlung sowie erhöhter Mortalität in Verbindung gebracht. Eine Verständnislosigkeit hinsichtlich der entsprechenden Pathomechanismen führt zu einem dringenden medizinischen Bedarf für effektive diagnostische Hilfsmittel und Behandlungen. Das Ziel des EU-finanzierten Forschungsprojekts BioCog ist daher die Entwicklung eines Diagnoseinstruments für die klinische Anwendung, das postoperatives Delirium und postoperative kognitive Dysfunktion vorzeitig erkennt. Dieses Projekt wird hoffentlich eine große Lücke zwischen Nachweis und patientenorientierten Ergebnissen schließen.

1. Introduction

Cognitive impairment is increasingly prevalent in our aging society. Neurodegenerative illnesses, like dementia, are certainly frequent causes, however, a number of additional factors can also play a key role. One major factor is the occurrence of so-called acute Post-Operative Delirium (POD, DSM-V: 293.0) followed by Chronic Post-Operative Cognitive Dysfunction (POCD, DSM-V: 294.10). The incidence of POD/POCD after elective, non-cardiac surgery varies between 4 – 54 %; POD/POCD incidence is even higher in cardiac surgery patients. Unlike acute POD, chronic POCD tends to persist over time.

In the EU-funded ISPOCD1 study, the largest study of POD/POCD to date which was conducted in the early 1990s, POCD incidences were reported for N = 948 non-cardiac surgical patients. Cognitive function was assessed at the 3-month follow-up. Functional decline

The video of presentation is shown online:

(cognitive deficits measured by a composite score for memory and/or attention tasks in a neuropsychological test battery) occurred in 19 % of individuals with no previously documented case of delirium, in 32 % after a short period of delirium (1 – 2 days), and in 55 % after a more prolonged episode of delirium. In elderly patients, POCD resembles chronic dementia and appears to accelerate the cognitive decline in pre-existing Alzheimer dementia. In a recent meta-analysis, an odds ratio = 12.52 [95 % CI, 1.86-84.21] was reported for the association of postoperative delirium and the subsequent development of dementia after a 3.2 and 5.0 year follow-up (corrected for baseline dementia, severity of illness, age). A significant association between POD and mortality was also found after a mean follow-up at 11.4 months (OR = 1.71 [95 % CI, 1.27–2.30]). POD/POCD risk in an individual patient depends on a number of sociodemographic and clinical factors, including age, pre-existing (insidious) dementia, inflammatory and metabolic conditions etc. In addition, the surgical procedure itself is a risk factor that is related to the duration of the surgical intervention, anesthesia and perioperative medical complications. Thus, while a surgical procedure can be successful (from the perspective of the surgeon), the price the patient has to pay can be very high when dementia is the outcome. Moreover, in aging societies, such as industrialized European nations, the socioeconomic implications of postoperative cognitive impairment are also profound: POD/POCD is associated with longer and more costly hospital treatment, increased mortality, and dependency on social transfer payments.

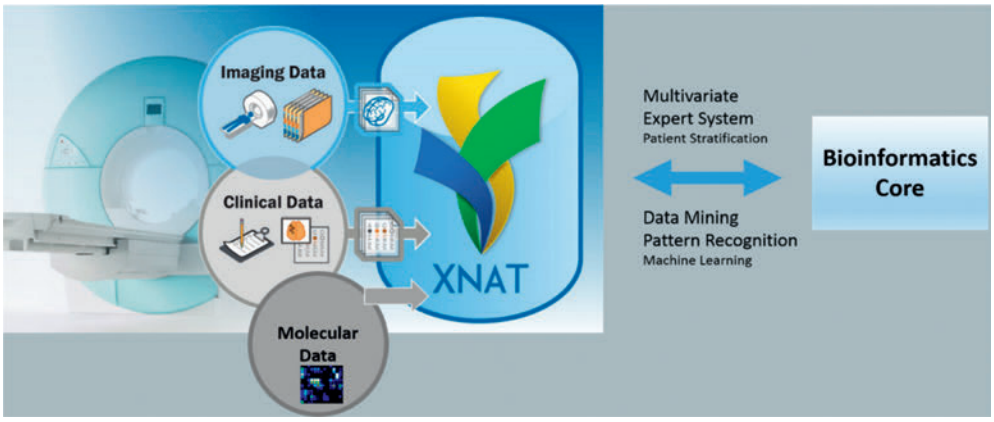

Fig. 1 Database administration structure

Needless to say, there is an urgent medical need that must be addressed: We need better risk-to-benefit assessments in the decision-making process before surgical interventions are carried out – assessments which also include a patient's risk of developing dementia after the operative procedure. In addition, perioperative treatment schemes need to be developed in order to minimize the occurrence of cognitive impairment. To achieve these goals, it will be necessary to considerably improve our still sketchy knowledge of POD/POCD. In particular, we need to be able to predict individual risk before surgery and to understand the pathophysiological processes and molecular cascades which lead to POD/POCD. At present, two large international studies are underway to address the pathophysiological and molecular basis of

POD/POCD: the *SAGES study* at Harvard and the *BioCog study* in Europe. The BioCog study is coordinated by the Charité and includes twelve academic and private partners throughout Europe.

2. BioCog: Biomarker Development for Postoperative Cognitive Impairment in the Elderly

Goal of the study: The European Research & Development (R&D) Consortium BioCog will establish valid neuroimaging and biomarker panels for risk/clinical outcome prediction of POD/POCD (Postoperative Delirium/Postoperative Cognitive Dysfunction). The primary goal of the BioCog project is to deliver a diagnostic tool for clinical practice to predict POD/POCD risk in patients who are scheduled for major elective surgery.

Study design: Observational cohort study. The study population will be 1,200 patients, aged 65 to 85 undergoing major elective surgery. Patient recruitment started in 1/2015 and will be completed by July 2017. Patient recruitment sites: Charité (CVK, CCM), Utrecht University Hospital. Repeated investigations (clinical, neuropsych, imaging, molecular) are conducted at multiple time points pre- and post-operatively with long-term follow-up (3 and 12 months, planned 3 years).

Databank: The databank consists of three parts: clinical, molecular, neuroimaging.

- ***Clinical databank (eCRF)***: Medical history, medical status inclusive medication status, neuropsychological testing. Databank administration software: SecuTrial – validated, compliant with 21 CFR Part 11 (FDA).
- ***Molecular databank***: Peripheral markers (proteins, metabolites etc.), blood genome (Next Generation Sequencing, NGS), transcriptome (mRNA, miRNA microarray) – validation with cerebrospinal fluid/post mortem (brain). Databank administration software: CentraXX (certification ongoing).

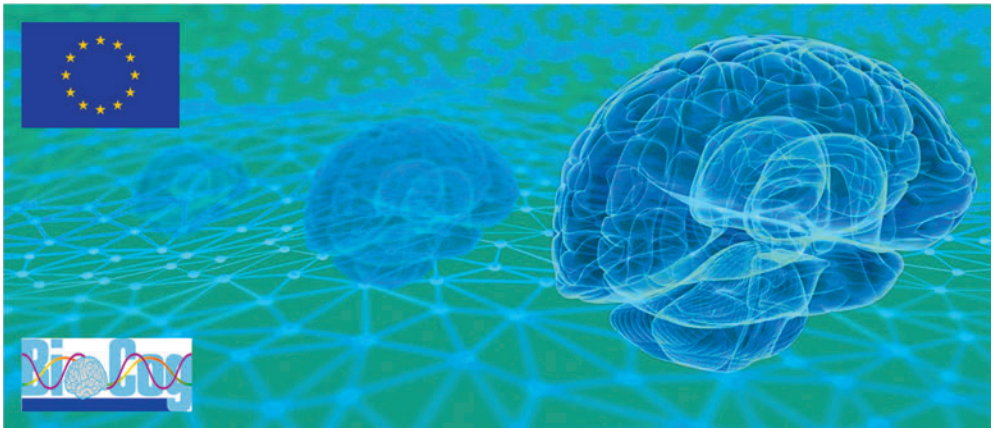

Fig. 2 Individual risk prediction using deep learning algorithms

– ***Neuroimaging Databank***: T1 (volume/3D), resting fMRI with simultaneous EEG, T2 SPACE, T2 HighRes Hippo, ASL, DTI. Databank administration software: XNAT – validated, compliant with 21 CFR Part 11 (FDA). The neuroinformatics platform XNAT also allows the integration and administration of neuroimaging, clinical and molecular data.

Data analysis: A 2-step procedure is used for multivariate data analysis (developing a classifier for risk prediction):

– ***Training set*:** Data of the first N = 400 patients serve as a training set to establish the statistical analysis procedures for the different data domains (clinical, neuropsych, molecular, neuroimaging) using multivariate discriminant and regression analyses as well as state-of-the art machine learning algorithms (support vector machines, artificial neural networks). For machine learning, we are primarily using the open source software package TensorFlow (Google Brain).
– ***Test set*:** Data on the remaining N = 800 patients are then used as a test set.
– ***Health economics analysis*:** Health economics data, collected as part of the BioCog project, will ultimately be used to provide cost estimates for the potential impact of the newly created diagnostic tool in clinical practice, i.e. decision-making process (purchasing decision) for or against prescribing/performing a surgical intervention.

Current status: Patient recruitment: N > 900 patients have been enrolled in the study. Last patient to be enrolled by 6/2017. Currently completing set-up of databank administration software CentraXX and XNAT by 4/2017. Currently completing data curating of clinical bank SecuTrial by 2/2017. First pilot analyses (clinical, neuropsych, molecular inclusive microarray, neuroimaging) using the training set (N = 400) are currently underway. Statistical analysis plan (SAP) currently being refined. First results expected in summer 2017.

Outlook: We expect to be able to present/provide the public with the first algorithms for individual risk prediction ("personalized medicine") as early as 2018/2019 so that patient care can be improved.

Funding: BioCog has received 6 million EUR in funding from the European Union since 2014 within the framework of the 7th research program, grant agreement no. 602461. In addition, the Berlin Institute of Health (BIH), a common research platform of the Charité Berlin and the Berlin Helmholtz Institute Max-Delbrück Center (MDC), is funding the BioCog project as a so-called pathfinder study. An international patent application is currently being filed. A grant application to obtain additional funding from the BMBF is currently underway to conduct long-term follow-up investigations (3 years post-OP).

Prof. Dr. med. Georg Winterer
BioCog Consortium Coordinator
Experimental and Clinical Research Center (ECRC)
Department of Anesthesiology & Intensive Care Medicine
Charité – Universitätsmedizin Berlin
ECRC, Campus Buch
Lindenberger Weg 80
13125 Berlin
Germany
Tel.: +49 30 450540105
Fax: +49 30 4507540540
E-Mail: georg.winterer@charite.de
www.biocog.eu

Nova Acta Leopoldina NF Nr. *421*, 127–131 (2018)

Perioperative Optimization and Postoperative Outcomes: From Alpha to Omega

Michael Sander (Giessen)

Abstract

Perioperative goal-directed hemodynamic therapy (PGDT) in high-risk surgical patients can improve outcomes, lower postoperative morbidity and mortality, and reduce additional costs. However, optimized monitoring technology and treatment protocols have yet to be established. There is an obvious need for major randomized multi-center studies to finally find the best monitoring tool and treatment algorithm to improve short- and long-term patient-centered outcomes.

Zusammenfassung

Perioperative zielorientierte hämodynamische Therapie bei chirurgischen Patienten mit hohem Risiko kann Ergebnisse verbessern, postoperative Morbidität und Mortalität verringern und zusätzliche Kosten senken. Dennoch müssen optimierte Überwachungstechnologien und Behandlungsprotokolle geschaffen werden. Es gibt einen offenkundigen Bedarf an großen randomisierten Multicenter-Studien, damit schließlich das beste Überwachungsinstrument und der beste Behandlungsalgorithmus gefunden werden können, um patientenorientierte Kurz- und Langzeitergebnisse zu verbessern.

1. Introduction

Perioperative goal-directed hemodynamic therapy (PGDT) has been promoted for almost three decades now as a state-of-the-art intervention for high-risk surgical patients. It is thought to improve outcomes, reduce postoperative morbidity and mortality, and be a potential cost-effective intervention that might also reduce costs for the hospital and society (Michard et al. 2015, Navarro et al. 2015, Hamilton et al. 2011, Grocott et al. 2013, Pearse et al. 2014, Manecke et al. 2014). One of the first studies done in the field was published in the last century by Shoemaker et al. (1988) as a way to optimize oxygen delivery to high-risk patients undergoing major surgery. Shoemaker's study was able to show that when high-risk patients underwent preoperative optimization using a pulmonary artery catheter, complications and mortality went down compared to a control group. Early single centre studies also showed promising results, even with respect to potential long-term effects (Boyd et al. 1993, Rhodes et al. 2010).

The video of presentation is shown online:

2. Does Goal-Directed Hemodynamic Management Improve Outcomes?

A multitude of studies have been published that combine this concept with different monitoring technology, algorithms and patient cohorts. Most show improvement in postoperative complication rates and length of hospital stay (Pearse et al. 2005, Scheeren et al. 2013, Salzwedel et al. 2013, Benes et al. 2010, Goepfert et al. 2013, Pearse et al. 2014). These findings were published in several meta analyses and Cochrane reviews (Ripollés-Melchor et al. 2016, Rollins and Lobo 2016, Grocott et al. 2012, Hamilton et al. 2011, Pearse et al. 2014, Benes et al. 2014). Some negative studies have also been published (Schmid et al. 2016, Challand et al. 2012). However, most of these negative studies highlight some important limitations of the PGDT concept that need to be discussed. The most important thing to note with PGDT is that monitoring alone does not improve outcomes (Vincent et al. 2011, 2015, Cecconi et al. 2014). A further important point that needs acknowledging is that the patients being studied have to be at risk for postoperative complications. When the PGDT concept is studied in very low risk patients undergoing minor surgery, there is no or only a minor chance of detecting benefits (Cecconi et al. 2013, Challand et al. 2012, Cecconi et al. 2011). Another important issue is monitoring technology. The chance of PGDT improving important outcomes is diminished if the applied monitoring technology is unable to detect the degree of change in, for instance, stroke volume that would be necessary to trigger an intervention (Cecconi and Rhodes 2014, Pestaña et al. 2014). Therefore, an ideal monitoring tool should be able to provide accurate and precise measurements with good trending ability and in real time, i.e. beat-to-beat. The choice of the "right" monitor depends on the expertise of the user, the patient population and the clinical pathway, where goal-directed monitoring should be applied (Ramsingh et al. 2012).

Another point of discussion is the use of inotropic drugs within PGDT algorithms. At the moment no studies are able to sufficiently address whether this is beneficial or harmful and whether inotropic agents should be titrated to the, somehow, defined individual needs of the patient. Several studies and meta-analyses have specifically looked at this question and have found no increased harm and some benefit with inotrope use in addition to fluid optimization (Arulkumaran et al. 2014, Hamilton et al. 2011). However, there is data that backs the idea that increased use of inotropic drugs in high-risk patients might bring some additional risk for the patient (Tacon et al. 2012, Mebazaa et al. 2010, Schwann et al. 2011, Nielsen 2014). The aim of using inotropic agents is to improve microcirculation and increase global cardiac output to accommodate the additional needs during and after surgery (Pearse et al. 2008, Jhanji et al. 2010). One part of this unproven concept is to increase oxygen delivery to such an extent that oxygen delivery/oxygen uptake (DO_2/VO_2) dependence can be dispensed with. At present this is, however, hard to individualize since routine and even moderately advanced parameters, like venous saturation monitoring, are unable to predict VO_2 responders (Monnet et al. 2013). Therefore, cardiac output/cardiac index goals are currently somewhat artificial, as they are usually not tailored to the individual patient in standard PGDT protocols.

In conclusion, there is a need for a major, adequately powered randomized multi-centre study with an appropriate algorithm and an appropriate high-risk patient population that finally demonstrates the full and real potential benefit of this intervention.

References

Arulkumaran, N., Corredor, C., Hamilton, M. A., Ball, J., Grounds, R. M., Rhodes, A., and Cecconi, M.: Cardiac complications associated with goal-directed therapy in high-risk surgical patients: a meta-analysis. Br. J. Anaesth. *112*/4, 648–659 (2014)

Benes, J., Chytra, I., Altmann, P., Hluchy, M., Kasal, E., Svitak, R., Pradl, R., and Stepan, M.: Intraoperative fluid optimization using stroke volume variation in high risk surgical patients: results of prospective randomized study. Crit. Care (London, England) *14*/3, R118 (2010)

Benes, J., Giglio, M., Brienza, N., and Michard, F., et al.: The effects of goal-directed fluid therapy based on dynamic parameters on post-surgical outcome: a meta-analysis of randomized controlled trials. Crit. Care (London, England) *18*/5, 584 (2014)

Boyd, O., Grounds, R. M., and Bennett, E. D.: A Randomized clinical trial of the effect of deliberate perioperative increase of oxygen delivery on mortality in high-risk surgical patients. JAMA *270*/22, 2699–2707 (1993)

Cecconi, M., Backer, D. de, Antonelli, M., Beale, R., Bakker, J., Hofer, C., Jaeschke, R., Mebazaa, A., Pinsky, M. R., Teboul, J. L., Vincent, J. L., and Rhodes, A.: Consensus on circulatory shock and hemodynamic monitoring. Task force of the European Society of Intensive Care Medicine. Intensive Care Med. *40*/12, 1795–1815 (2014)

Cecconi, M., Corredor, C., Arulkumaran, N., Abuella, G., Ball, J., Grounds, R. M., Hamilton, M., and Rhodes, A.: Clinical review: Goal-directed therapy – what is the evidence in surgical patients? The effect on different risk groups. Crit. Care (London, England) *17*/2, 209 (2013)

Cecconi, M., Fasano, N., Langiano, N., Divella, M., Costa, M. G., Rhodes, A., and Della Rocca, G.: Goal-directed haemodynamic therapy during elective total hip arthroplasty under regional anaesthesia. Crit. Care (London, England) *15*/3, R132 (2011)

Cecconi, M., and Rhodes, A.: Goal-directed therapy: time to move on? Anesthesia and Analgesia *119*/3, 516–518 (2014)

Challand, C., Struthers, R., Sneyd, J. R., Erasmus, P. D., Mellor, N., Hosie, K. B., and Minto, G.: Randomized controlled trial of intraoperative goal-directed fluid therapy in aerobically fit and unfit patients having major colorectal surgery. Br. J. Anaesth. *108*/1, 53–62 (2012)
Available at:
http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?dbfrom=pubmed&id=21873370&retmode=ref&cmd=prlinks

Goepfert, M. S., Richter, H. P., Zu Eulenburg, C., Gruetzmacher, J., Rafflenbeul, E., Roeher, K., Sandersleben, A. von, Diedrichs, S., Reichenspurner, H., Goetz, A. E., and Reuter, D. A.: Individually optimized hemodynamic therapy reduces complications and length of stay in the intensive care unit: a prospective, randomized controlled trial. Anesthesiology *119*/4, 824–836 (2013)

Grocott, M. P., Dushianthan, A., Hamilton, M. A., Mythen, M. G., Harrison, D., Rowan, K., and *Optimisation Systematic Review Steering Group*: Perioperative increase in global blood flow to explicit defined goals and outcomes following surgery. Cochrane Database Syst. Rev. (Online), *11*, p. CD004082 (2012)

Grocott, M. P., Dushianthan, A., Hamilton, M. A., Mythen, M. G., Harrison, D., Rowan, K., and *Optimisation Systematic Review Steering Group*: Perioperative increase in global blood flow to explicit defined goals and outcomes after surgery: a Cochrane Systematic Review. Br. J. Anaesth. *111*/4, 535–548 (2013)

Hamilton, M. A., Cecconi, M., and Rhodes, A.: A systematic review and meta-analysis on the use of preemptive hemodynamic intervention to improve postoperative outcomes in moderate and high-risk surgical patients. Anesthesia and Analgesia *112*/6, 1392–1402 (2011)

Jhanji, S., Vivian-Smith, A., Lucena-Amaro, S., Watson, D., Hinds, C. J., and Pearse, R. M.: Haemodynamic optimisation improves tissue microvascular flow and oxygenation after major surgery: a randomised controlled trial. Crit. Care (London, England) *14*/4, R151 (2010)

Manecke, G. R., Asemota, A., and Michard, F.: Tackling the economic burden of postsurgical complications: would perioperative goal-directed fluid therapy help? Crit. Care (London, England) *18*/5, 864 (2014)

Mebazaa, A., Parissis, J., Porcher, R., Gayat, E., Nikolaou, M., Boas, F. V., Delgado, J. F., and Follath, F.: Short-term survival by treatment among patients hospitalized with acute heart failure: the global ALARM-HF registry using propensity scoring methods. Intensive Care Med. *37*/2, 290–301 (2010)

Michard, F., Mountford, W. K., Krukas, M. R., Ernst, F. R., and Fogel, S. L.: Potential return on investment for implementation of perioperative goal-directed fluid therapy in major surgery: a nationwide database study. Perioper. Med. (London, England) *4*/1, 497 (2015)

Monnet, X., Julien, F., Ait-Hamou, N., Lequoy, M., Gosset, C., Jozwiak, M., Persichini, R., Anguel, N., Richard, C., and Teboul, J. L.: Lactate and venoarterial carbon dioxide difference/arterial-venous oxygen difference ratio, but not central venous oxygen saturation, predict increase in oxygen consumption in fluid responders. Critical Care Medicine *41*/6, 1412–1420 (2013)

Navarro, L. H. C., Bloomstone, J. A., Auler, J. O. Jr., Cannesson, M., Rocca, G. D., Gan, T. J., Kinsky, M., Magder, S., Miller, T. E., Mythen, M., Perel, A., Reuter, D. A., Pinsky, M. R., and Kramer, G. C.: Perioperative fluid therapy: A statement from the international Fluid Optimization Group. Perioper. Med. (London, England) *4*, 3 (2015)

Nielsen, D.: Health outcomes with and without use of inotropic therapy in cardiac surgery: Results of a propensity score-matched analysis. Anesthesiology *120*/5, 1098–1108 (2014)

Pearse, R. M., Belsey, J. D., Cole, J. N., and Bennett, E. D.: Effect of dopexamine infusion on mortality following major surgery: Individual patient data meta-regression analysis of published clinical trials. Crit. Care Med. *36*/4, 1323–1329 (2008)

Pearse, R., Dawson, D., Fawcett, J., Rhodes, A., Grounds, R. M., and Bennett, E. D.: Early goal-directed therapy after major surgery reduces complications and duration of hospital stay. A randomised, controlled trial [ISRCTN38797445]. Crit. Care (London, England) *9*/6, R687–693 (2005)

Pearse, R. M., Harrison, D. A., MacDonald, N., Gillies, M. A., Blunt, M., Ackland, G., Grocott, M. P., Ahern, A., Griggs, K., Scott, R., Hinds, C., Rowan, K., and *OPTIMISE Study Group*: Effect of a perioperative, cardiac output-guided hemodynamic therapy algorithm on outcomes following major gastrointestinal surgery: A randomized clinical trial and systematic review. JAMA *311*/21, 2181–2190 (2014)

Pestaña, D., Espinosa, E., Eden, A., Nájera, D., Collar, L., Aldecoa, C., Higuera, E., Escribano, S., Bystritski, D., Pascual, J., Fernández-Garijo, P., Prada, B. de, Muriel, A., and Pizov, R.: Perioperative goal-directed hemodynamic optimization using noninvasive cardiac output monitoring in major abdominal surgery: a prospective, randomized, multicenter, pragmatic trial: POEMAS Study (PeriOperative goal-directed thErapy in Major Abdominal Surgery). Anesthesia and Analgesia *119*/3, 579–587 (2014)

Ramsingh, D., Alexander, B., and Cannesson, M.: Clinical review: Does it matter which hemodynamic monitoring system is used? Crit. Care (London, England) *17*/2, 208 (2012)

Rhodes, A., Cecconi, M., Hamilton, M., Poloniecki, J., Woods, J., Boyd, O., Bennett, D., and Grounds, R. M.: Goal-directed therapy in high-risk surgical patients: a 15-year follow-up study. Intensive Care Med. *36*/8, 1327–1332 (2010)

Ripollés-Melchor, J., Espinosa, Á., Martínez-Hurtado, E., Abad-Gurumeta, A., Casans-Francés, R., Fernández-Pérez, C., López-Timoneda, F., and Calvo-Vecino, J. M.: Perioperative goal-directed hemodynamic therapy in noncardiac surgery: a systematic review and meta-analysis. J. Clin. Anesth. *28*, 105–115 (2016)

Rollins, K. E., and Lobo, D. N.: Intraoperative goal-directed fluid therapy in elective major abdominal surgery: A meta-analysis of randomized controlled trials. Annals of Surgery *263*/3, 465–476 (2016)

Salzwedel, C., Puig, J., Carstens, A., Bein, B., Molnar, Z., Kiss, K., Hussain, A., Belda, J., Kirov, M. Y., Sakka, S. G., and Reuter, D. A.: Perioperative goal-directed hemodynamic therapy based on radial arterial pulse pressure variation and continuous cardiac index trending reduces postoperative complications after major abdominal surgery: a multi-center, prospective, randomized study. Crit. Care (London, England) *17*/5, R191 (2013)

Scheeren, T. W., Wiesenack, C., Gerlach, H., and Marx, G.: Goal-directed intraoperative fluid therapy guided by stroke volume and its variation in high-risk surgical patients: a prospective randomized multicentre study. J. Clin. Monit.Comput. *27*/3, 225–233 (2013)

Schmid, S., Kapfer, B., Heim, M., Bogdanski, R., Anetsberger, A., Blobner, M., and Jungwirth, B.: Algorithm-guided goal-directed haemodynamic therapy does not improve renal function after major abdominal surgery compared to good standard clinical care: a prospective randomised trial. Crit. Care (London, England) *20*/1, 50 (2016)

Schwann, N. M., Hillel, Z., Hoeft, A., Barash, P., Möhnle, P., Miao, Y., and Mangano, D. T.: Lack of effectiveness of the pulmonary artery catheter in cardiac surgery. Anesthesia and Analgesia *113*/5, 994–1002 (2011)

Shoemaker, W. C., Appel, P. L., Kram, H. B., Waxman, K., and Lee, T. S.: Prospective trial of supranormal values of survivors as therapeutic goals in high-risk surgical patients. Chest *94*/6, 1176–1186 (1988)

Tacon, C. L., McCaffrey, J., and Delaney, A.: Dobutamine for patients with severe heart failure: a systematic review and meta-analysis of randomised controlled trials. Intensive Care Med. *38*/3, 359–367 (2012)

Vincent, J.-L., Pelosi, P., Pearse, R., Payen, D., Perel, A., Hoeft, A., Romagnoli, S., Ranieri, V. M., Ichai, C., Forget, P., Della Rocca, G., and Rhodes, A.: Perioperative cardiovascular monitoring of high-risk patients: a consensus of 12. Crit. Care *19*/1 (London, England), 1–12 (2015)

Vincent, J.-L., Rhodes, A., Perel, A., Martin, G. S., Della Rocca, G., Vallet, B., Pinsky, M. R., Hofer, C. K., Teboul, J. L., Boode, W. P. de, Scolletta, S., Vieillard-Baron, A., Backer, D. de, Walley, K. R., Maggiorini, M., and Singer, M.: Clinical review: Update on hemodynamic monitoring – a consensus of 16. Crit. Care (London, England) *15*/4, 229 (2011)

Prof. Dr. Michael Sander
Department of Anaesthesiology
Intensive Care Medicine and Pain Therapy
Justus-Liebig-University
Rudolf-Buchheim-Straße 7
35392 Giessen
Germany
Tel.: +49 641 98544401
Fax: +49 641 98544409
E-Mail: Michael.Sander@chiru.med.uni-giessen.de

Nova Acta Leopoldina NF Nr. *421*, 133–134 (2018)

How to Improve Things: A Relative's Perspective

Nicci Gerrard (London, UK)

Abstract

John's Campaign advocates more compassionate and patient-centered care, particularly for patients with dementia. It has proven to be very successful: fewer falls, lower evidence of malnutrition and dehydration, faster discharge, slower re-admission and less cognitive decline. However, our Intensive Care Units (ICUs) often represent to the patient an unfamiliar environment, the lack of a loved one's face, a break from routines and a sense of insecurity. The task is to implement patient-centered care in our ICUs, as advocated by John's Campaign, in order to improve short- and long-term outcomes, particularly in dementia patients.

Zusammenfassung

Johns Kampagne setzt sich für eine einfühlsamere und patientenorientiertere Pflege ein, insbesondere bei Patienten mit Demenz. Sie hat sich als sehr erfolgreich erwiesen: weniger Stürze, weniger Hinweise auf Fehlernährung und Dehydration, schnellere Entlassungen, langsamere Rückübernahmen und geringerer Abbau der kognitiven Fähigkeiten. Dennoch stellen unsere Intensivpflegestationen oft eine unvertraute Umgebung für den Patienten dar, das Fehlen des Gesichts einer geliebten Person, eine Unterbrechung der Routine und ein Unsicherheitsgefühl. Die Aufgabe besteht darin, wie durch Johns Kampagne initiiert, patientenorientierte Pflege auf unseren Intensivpflegestationen umzusetzen, um Kurz- und Langzeitergebnisse, insbesondere bei Demenzpatienten, zu verbessern.

My father died two years and three months ago on November 9, 2014. Two weeks later, I and my friend Julia Jones founded John's campaign. Like many campaigns, it was born out of personal sorrow and guilt: My father had lived with Alzheimer's for over a decade, but when he was admitted to the hospital with leg ulcers, restricted visiting hours and a subsequent outbreak of norovirus kept us from his bedside, and he went into a precipitate decline.

He entered the hospital continent, healthy, mobile, articulate and happy; he came out incontinent, skeletal, unable to take a single step or even sit up in bed or lift a spoon to his mouth, and unable to piece words together into phrases or sentences. His leg ulcers were healed but his life was ruined. He lived for another nine months but never recovered. What I learned from this experience is that hospital stays are hazardous for those living with de-

The video of presentation is shown online:

mentia, and that there can be catastrophic results when loved ones are prevented from being with them, helping to feed them, keeping them mobile, talking with them, and keeping them connected to their world.

John's campaign is a very simple, single-issue campaign but it opens a window into a whole world of more compassionate and person-centered care. It asks that carers of those with dementia have the same rights to accompany them to the hospital as parents of sick children. There should be unrestricted access. Further, we ask that carers not simply be allowed, but be *welcomed* as part of the team of support around the patient, who may be confused and scared and who needs a familiar face and a person to act as their voice and their memory. The evidence now being gathered about the benefits that such unrestricted access brings seems robust: falls are fewer, there is less incidence of malnutrition and dehydration, discharges happen more swiftly and re-admission more slowly. Above all, the decline in cognitive functioning is less steep.

The campaign has been widely successful in the UK, yet there is more left to do: over 400 hospitals have signed up to it and it is part of the inspection criteria. National Health Service (NHS) staff support it and charities too. Simple as it is, it goes to the heart of what hospitals signify, at a time when a system that was set up to deal with acute health crises now has to deal with patients who have multiple conditions and may be in the hospital for weeks and months at a time. In the UK, nearly one in three beds are now occupied by a person with dementia. Hard-pressed nurses and doctors simply cannot cope with the demands this places upon them. A person with advanced dementia may require almost constant attention. The levels of distress can be huge.

Hospitals are bureaucratic and are often intimidating, medicalized spaces full of experts and rules. This environment can place a heavy toll on a person with dementia. The mind is a precarious thing, mysterious and too easily ruptured. The mind of a person with dementia is infinitely more precarious. An unfamiliar environment, the lack of a loved-one's face, a break from routines and the feeling of being unsafe can do massive and irrecoverable damage. A leg may be set, a leg ulcer cured, an infection brought under control, but a life may be ruined.

Nicci Gerrard
John's Campaign
E-Mail: nicci.gerrard@icloud.com

Innovations in Intensive Care Medicine, Perspectives from the Industry

Nova Acta Leopoldina NF Nr. *421*, 137–142 (2018)

Patient-Centered Innovation in Intensive Care Medicine – Hemodynamic Monitoring (Edwards Lifesciences Services GmbH)

Christoph Raspé (Halle/Saale)

Abstract

Hemodynamic goal-directed therapy (HGDT) using appropriate technical equipment, especially in high-risk patients, provides optimal tissue perfusion and oxygenation and has been shown to reduce perioperative morbidity and mortality. Despite this, it has yet to be implemented in clinical routine since final evidence remains outstanding. Besides its proven short-term effects, further research is urgently needed to study the impact of HGDT on patient-centered outcome parameters, i.e. neurocognitive deficits, functional rehabilitation, psychosocial restrictions, quality of life and patient satisfaction.

Zusammenfassung

Eine zielgerichtete hämodynamische Therapie, insbesondere bei Hochrisikopatienten, bietet eine optimale Gewebedurchblutung und Sauerstoffanreicherung und hat sich als wesentlich für die Senkung perioperativer Morbidität und Mortalität erwiesen. Trotzdem wurde sie noch nicht in den Klinikalltag umgesetzt. Neben den schon nachgewiesenen Kurzzeitwirkungen ist darüber hinaus weitere Forschung dringend notwendig, um die Auswirkungen einer zielgerichteten hämodynamischen Therapie auf patientenorientierte Ergebnisparameter, d. h. neurokognitive Ausfälle, funktionelle Rehabilitation, psychosoziale Einschränkungen, Lebensqualität und Patientenzufriedenheit, zu untersuchen.

The perioperative risk for patients is the subject of ongoing research and is of great importance for intensive care medicine. According to the *European Surgical Outcome Study*, jointly initiated by the European Society of Anaesthesiology (ESA) and European Society of Intensive Medicine (ESICM), perioperative mortality in Germany is 2.5 % (Pearse et al. 2012) despite all efforts and advances in intensive care medicine. This is mainly due to a small subpopulation of high-risk patients, which accounts for more than 3/4 of all perioperative fatalities (Pearse et al. 2006). In the coming years, the higher proportion of elderly people in the overall population due to demographic changes and the willingness to perform major surgery, even on multimorbid patients of an advanced age, will lead to an increase in high-risk intensive care patients. Therefore, it is particularly important to detect these high-risk patients in daily clinical practice. The basic prerequisite for this is the clinical evaluation of the patient by an experienced intensive care medical specialist (Ponikowski et al. 2016).

Once the high-risk population has been identified, the intensive care specialist should endeavor to achieve optimal tissue perfusion and oxygenation in these patients or to use therapeutic intervention to influence these parameters as much as possible (Janssens et al. 2016). The basic principle consists in optimizing the ratio between O_2 supply (DO_2) and con-

sumption (VO_2). The hypothesis underlying this is that an increase in DO_2 to normal values prevents a global or regional O_2 debt and thus anticipates the rise in O_2 demand as a result of the surgical trauma (Weyland and Scheeren 2012). Goal-directed therapy (GDT) conceptually embraces this principle. By also expanding monitoring parameters, efforts are being made to individually optimize DO_2 for the patients in the perioperative setting. The objective of GDT is therefore to prevent a global or regional O_2 debt during the perioperative phase through goal-directed, adapted volume therapy and, if necessary, to administer positively inotropic substances in order to reduce perioperative morbidity and mortality (Weyland and Scheeren 2012).

There are numerous expanded monitoring techniques that provide surrogate parameters for tissue perfusion and oxygenation, while allowing for limitations inherent to the method. The term monitoring stands for the repeated or continuous real-time recording of a range of physiological functions of a patient (Janssens et al. 2016). Expanded monitoring supplements basic monitoring by providing information about hemodynamic determinants related to flow, volume or metabolism. These include cardiac output, cardiac preload and afterload, mixed or central venous O_2 saturation as well as regional tissue oxygenation parameters (Weyland and Scheeren 2012). An important aspect of the various hemodynamic monitoring techniques is the possibility of continuous surveillance since this affords the opportunity to recognize and evaluate changes in hemodynamics and to immediately implement the therapeutic intervention options it suggests without delay. In the further course of treatment, hemodynamic monitoring allows the success of this intervention to be evaluated (Marx 2010). The intensive care medical specialist should therefore give due consideration to the differentiated monitoring methods available so that the "right" method is chosen for the "right" patient based on the situation at hand (Janssens et al. 2016). Currently there is no single ideal monitoring technique that meets all the requirements of hemodynamic surveillance. The choice of technique and its application should be patient-oriented, and the results should be interpreted in the clinical context (Janssens et al. 2016). Furthermore, the time, effort, invasiveness and potential benefits and risks for the patient should be weighed when deciding which technique to employ. The objective of hemodynamic monitoring also plays a central role in this respect (Janssens et al. 2016).

Currently no study demonstrates that a prognosis can be improved based solely on a monitoring technique or fixed target values. Meaningful monitoring can only improve a patient's prognosis if the measured data is integrated into individual therapeutic measures that achieve clinical benefits for the patient (Janssens et al. 2016). Only measuring hemodynamic parameters does nothing to change the outcome for the patient. However, measuring these parameters does permit continuous standardized GDT, the application of which may represent the decisive difference for the patient. Thus the physician plays a central role in interpreting the measured results (Marx 2010). GDT data for high-risk patients have significantly lowered the rate of complications and the repeat surgery rate, increased the protective effects on renal, pulmonary and cardiovascular organ function, reduced the length of the hospital stay and reduced morbidity and mortality (Salzwedel et al. 2013, Goepfert et al. 2013, Cecconi et al. 2013, Osawa et al. 2016). At the same time, some meta-analyses and prospectively randomized studies have been unable to confirm these positive results (Pearse et al. 2014, Peake et al. 2014). Thus, the data situation with regard to the formal criteria of evidence-based medicine is too heterogeneous to clearly and unequivocally recommend the use of a special technique or parameter of expanded hemodynamic monitoring to treat critically ill patients

(Reuter 2011/2012). Evidence-based recommendations for using hemodynamic monitoring currently do exist for intensive care related to heart surgery and internal medicine (Janssens et al. 2016).

In recent years, the expression "patient-oriented outcome", in conjunction with the growing interest in quality of life and against the backdrop of health policies, has developed into an important criterion with respect to the evaluation of therapies. In this context, the evaluation of quality of life covers a broad spectrum. The category encompasses not only symptoms and physical functionality, but also social and emotional concerns, well-being and the patient's general satisfaction with life. Thus, the treatment focus of goal-directed hemodynamic therapy should no longer be placed on acute care alone but also on the long-term impact on the quality of life. Accordingly, a complete assessment that includes a realistic survey of outcomes can only be made by combining patient-centered and investigator-centered measurement methods. With respect to patient-centered outcome parameters, such as neurocognitive deficits, functional rehabilitation, psychosocial restrictions, quality of life and patient satisfaction, existing data is currently inadequate for goal-directed hemodynamic therapy. Nevertheless, individual studies suggest that goal-directed hemodynamic therapy can also positively affect the quality of life of high-risk patients (Ebm et al. 2014, Rhodes et al. 2010). The S3 guideline for managing delirium, analgesia and sedation in intensive care medicine (Baron et al. 2015) recommends maintaining adequate cerebral perfusion to ensure stable systemic hemodynamics and to avoid neurocognitive deficits. Whether, in this context, positive effects on the neurological outcome can be achieved in intensive-care patients by implementing more extensive hemodynamic monitoring is currently the subject of ongoing studies (ClinicalTrials.gov: NCT01827501)

Interestingly, the existing evidence that high-risk surgical patients may benefit from hemodynamic monitoring both intraoperatively and postoperatively has yet to be implemented extensively in daily perioperative practice and application rates have not increased significantly in recent years (Marx 2010, Oldner et al. 2003, Funcke et al. 2016). One reason for this discrepancy is the fact that the prospects and the assessment of perioperative support are usually directed primarily at the condition of the patient at the end of the operation or of the stay in intensive care and less on the health evolution and the patient's well-being weeks or months after an operation (Weyland and Scheeren 2012). This focus on short-term effects, especially for at-risk patients, creates the false impression that perioperative support has proceeded "optimally" (Weyland and Scheeren 2012), even though circulatory dysbalances not detected and treated intraoperatively may have considerable consequences for the patient's long-term prognosis. Nevertheless, expanded hemodynamic monitoring may achieve early recognition of homeostasis disorders and, when the measured predictive parameters are used to direct physiologically based therapy, will contribute to an improvement in the postoperative outcome.

Technically speaking, easily portable, wireless, interface-compatible devices with a simple configuration are needed that can be used across all sectors (operating theatre, intensive-care unit, recovery room, intermediate care unit, emergency room). Universal and complication-free availability and operability could improve the degree of penetration and the acceptance of expanded hemodynamic monitoring, making its application for high-risk patients more widespread. At the same time, this could also achieve integral and seamless use of goal-directed hemodynamic therapy (e.g. emergency room to operating theatre to intensive care unit to intermediate care) and optimal patient-centered results. Improving the connectiv-

ity would facilitate the exchange and transfer of data between the hospital's electronic medical information system and the monitoring results, thereby mitigating the interface problem. Simplified device communication would permit individualized therapy that would be adapted to the patient's current condition and comorbidities.

With focus on the patient-centered outcome and individualized medical treatment adapted to the patient and to the general conditions, it becomes clear that the choice of monitoring technique and treatment algorithm must also be adapted in a patient-oriented manner and to the clinical context. This could be technically implemented by making a platform of hemodynamic monitoring available at each workstation that is compatible with all common monitoring techniques and therapeutic approaches and that seamlessly integrates future technologies. The platform would therefore offer a holistic view of the clinically confirmed measured parameters, enabling the free selection of the associated invasiveness stages. Harmonizing platform-based operation with an intuitive, more uniform user interface would improve user comfort and acceptance and hence monitoring efficiency, and, as a consequence, also the effectiveness of the therapeutic measures. The new HemoSphere hemodynamic platform from Edwards Lifesciences enables the basic technologies to be displayed on one monitor, together with the possibility of implementing future developments.

According to current data, one to two thirds of all hospitals use a documented treatment algorithm for goal-directed hemodynamic therapy (Funcke et al. 2016, Cannesson et al. 2011), although it is evident that only a protocol-based treatment has sustainably positive effects on patient outcomes. When algorithm adherence in hospitals with an established hemodynamic monitoring protocol is also considered, and the experience from studies on protocol adherence is transferred to goal-directed hemodynamic therapy from other areas, such as sepsis therapy (Ferrer et al. 2008), it becomes clear that the technical assistance of monitoring systems would be very useful and relevant for algorithm adherence. Colored indicators would indicate, at a glance, the patient's status and any deviations away from the specified therapy protocol. Rapidly changing clinical situations could be immediately identified so that a better-informed decision could be made. Thus the patient-centered outcome would be significantly improved by the universal ability to call up an individualized treatment algorithm and by helping to adhere to the protocol. Such forms of assistance are also integrated into the new HemoSphere hemodynamic platform from Edwards Lifesciences.

References

Baron, R., Binder, A., Biniek, R., Braune, S., Buerkle, H., Dall, P., Demirakca, S., Eckardt, R., Eggers, V., Eichler, I., Fietze, I., Freys, S., Fründ, A., Garten, L., Gohrbandt, B., Harth, I., Hartl, W., Heppner, H. J., Horter, J., Huth, R., Janssens, U., Jungk, C., Kaeuper, K. M., Kessler, P., Kleinschmidt, S., Kochanek, M., Kumpf, M., Meiser, A., Mueller, A., Orth, M., Putensen, C., Roth, B., Schaefer, M., Schaefers, R., Schellongowski, P., Schindler, M., Schmitt, R., Scholz, J., Schroeder, S., Schwarzmann, G., Spies, C., Stingele, R., Tonner, P., Trieschmann, U., Tryba, M., Wappler, F., Waydhas, C., Weiss, B., and Weisshaar, G.: Evidence and consensus based guideline for the management of delirium, analgesia, and sedation in intensive care medicine. Revision 2015 (DAS-Guideline 2015) – short version. Ger. Med. Sci. *13*, Doc19 (2015)

Cannesson, M., Pestel, G., Ricks, C., Hoeft, A., and Perel, A.: Hemodynamic monitoring and management in patients undergoing high risk surgery: a survey among North American and European anesthesiologists. Crit. Care *15*/4, R197 (2011)

Cecconi, M., Corredor, C., Arulkumaran, N., Abuella, G., Ball, J., Grounds, R. M., Hamilton, M., and Rhodes, A.: Clinical review: Goal-directed therapy – what is the evidence in surgical Patients? The effect on different risk groups. Crit. Care *17*/2, 209 (2013)

Ebm, C., Cecconi, M., Sutton, L., and Rhodes, A.: A cost-effectiveness analysis of postoperative goal-directed therapy for high-risk surgical patients. Crit. Care Med. *42*/5, 1194–1203 (2014)

Ferrer, R., Artigas, A., Levy, M. M., Blanco, J., González-Díaz, G., Garnacho-Montero, J., Ibáñez, J., Palencia, E., Quintana, M., de la Torre-Prados, M. V., and *Edusepsis Study Group*: Improvement in process of care and outcome after a multicenter severe sepsis educational program in Spain. JAMA *299*/19, 2294–2303 (2008)

Funcke, S., Sander, M., Goepfert, M. S., Groesdonk, H., Heringlake, M., Hirsch, J., Kluge, S., Krenn, C., Maggiorini, M., Meybohm, P., Salzwedel, C., Saugel, B., Wagenpfeil, G., Wagenpfeil, S., Reuter, D. A., and *ICU-CardioMan Investigators*: Practice of hemodynamic monitoring and management in German, Austrian, and Swiss intensive care units: the multicenter cross-sectional ICU-CardioMan Study. Ann. Intensive Care *6*, 49 (2016)

Goepfert, M. S., Richter, H. P., Zu Eulenburg, C., Gruetzmacher, J., Rafflenbeul, E., Roeher, K., Sandersleben, A. von, Diedrichs, S., Reichenspurner, H., Goetz, A. E., and Reuter, D. A.: Individually optimized hemodynamic therapy reduces complications and length of stay in the intensive care unit: a prospective, randomized controlled trial. Anesthesiology *119*/4, 824–836 (2013)

Janssens, U., Jung, C., und Hennersdorf, M.: Empfehlungen zum hämodynamischen Monitoring in der internistischen Intensivmedizin [Recommendations on hemodynamic monitoring in intensive care related to internal medicine]. Kardiologe *10*, 149–169 (2016)

Marx, G.: Hämodynamisches Monitoring – Nutzen oder Risiko für den Patienten? [Hemodynamic monitoring – Benefit or risk for the patient?] Intensivmed. *47*, 336–337 (2010)

Oldner, A., Rossi, P., Karason, S., Aneman, A., and *Scandinavian Critical Care Trials Group*: A practice survey on vasopressor and inotropic drug therapy in Scandinavian intensive care units. Acta Anaesthesiol. Scand. *47*, 693–701 (2003)

Osawa, E. A., Rhodes, A., Landoni, G., Galas, F. R., Fukushima, J. T., Park, C. H., Almeida, J. P., Nakamura, R. E., Strabelli, T. M., Pileggi, B., Leme, A. C., Fominskiy, E., Sakr, Y., Lima, M., Franco, R. A., Chan, R. P., Piccioni, M. A., Mendes, P., Menezes, S. R., Bruno, T., Gaiotto, F. A., Lisboa, L. A., Dallan, L. A., Hueb, A. C., Pomerantzeff, P. M., Kalil Filho, R., Jatene, F. B., Auler Junior, J. O., and Hajjar, L. A.: Effect of perioperative goal-directed hemodynamic resuscitation therapy on outcomes following cardiac surgery: A randomized clinical trial and systematic review. Crit. Care Med. *44*/4, 724–733 (2016)

Peake, S. L., Delaney, A., Bailey, M., Bellomo, R., Cameron, P. A., Cooper, D. J., Higgins, A. M., Holdgate, A., Howe, B. D., Webb, S. A., and Williams, P.: Goal-directed resuscitation for patients with early septic shock. New Engl. J. Med. *371*, 1496–1506 (2014)

Pearse, R. M., Harrison, D. A., James, P., Watson, D., Hinds, C., Rhodes, A., Grounds, R. M., and Bennett, E. D.: Identification and characterization of the high-risk surgical population in the United Kingdom. Crit. Care *10*/3, R81 (2006)

Pearse, R. M., Harrison, D. A., MacDonald, N., Gillies, M. A., Blunt, M., Ackland, G., Grocott, M. P., Ahern, A., Griggs, K., Scott, R., Hinds, C., Rowan, K., and *OPTIMISE Study Group*: Effect of perioperative, cardiac output-guided hemodynamic therapy algorithm on outcomes following major gastrointestinal surgery. JAMA *311*/21, 2181–2190 (2014)

Pearse, R. M., Moreno, R. P., Bauer, P., Pelosi, P., Metnitz, P., Spies, C., Vallet, B., Vincent, J. L., Hoeft, A., Rhodes, A., and *European Surgical Outcomes Study (EuSOS) Group for the Trials Groups of the European Society of Intensive Care Medicine and the European Society of Anaesthesiology*: Mortality after surgery in Europe: a 7 day cohort study. Lancet *380*/9847, 1059–1065 (2012)

Ponikowski, P., Voors, A. A., Anker, S. D., Bueno, H., Cleland, J. G., Coats, A. J., Falk, V., González-Juanatey, J. R., Harjola, V. P., Jankowska, E. A., Jessup, M., Linde, C., Nihoyannopoulos, P., Parissis, J. T., Pieske, B., Riley, J. P., Rosano, G. M., Ruilope, L. M., Ruschitzka, F., Rutten, F. H., van der Meer, P., and *Authors/Task Force Members, Document Reviewers*: ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. Eur. J. Heart Fail. *18*/8, 891–975 (2016)

Reuter, D.: Herz-Kreislauf-Monitoring – Was ist Evidenz-basiert? [Cardiocirculatory monitoring – What is evidence-based?] DIVI Jahrbuch [Yearbook of the German Interdisciplinary Association for Intensive Care and Emergency Medicine] 2011/2012: Interdisziplinäre Intensivmedizin und Notfallmedizin [Interdisciplinary Intensive Care and Emergency Medicine] 177–186 (2011/2012)

Rhodes, A., Cecconi, M., Hamilton, M., Poloniecki, J., Woods, J., Boyd, O., Bennett, D., and Grounds, R. M.: Goal-directed therapy in high-risk surgical patients: a 15-year follow-up study. Intensive Care Med. *36*/8, 1327–1332 (2010)

Salzwedel, C., Puig, J., Carstens, A., Bein, B., Molnar, Z., Kiss, K., Hussain, A., Belda, J., Kirov, M. Y., Sakka, S. G., and Reuter, D. A.: Perioperative goal-directed hemodynamic therapy based on radial arterial pulse pressure variation and continuous cardiac index trending reduces postoperative complications after major abdominal surgery: a multi-center, prospective, randomized study. Crit. Care *17*/5, R191 (2013)

Weyland, A., and Scheeren, T.: Effects of advanced haemodynamic monitoring on perioperative outcome in high-risk patients. Anästhesiol. Intensivmed. Notfallmed. Schmerzther. *47*/2, 92–100 (2012)

Prof. Dr. med. Christoph Raspé
Department of Anesthesiology and Critical Care Medicine
Halle-Wittenberg University
Ernst-Grube-Straße 40
06120 Halle (Saale)
Germany
Tel.: +49 345 5572322
Fax: +49 345 5571800
E-Mail: christoph.raspe@uk-halle.de

Nova Acta Leopoldina NF Nr. *421*, 143–148 (2018)

Patient-Centered Innovations for Intensive Care Medicine (Philips Healthcare)

Thomas Falck, Jacco Eerden and Gaby Meekes
(Eindhoven, The Netherlands)

Abstract

Philips is focusing its technical innovations on patient-centered outcomes. The vision is to provide patient-centered care by creating an environment that does not cause stress or anxiety in the patient and produces the highest possible quality-of-life after the patient is discharged from the hospital. This includes not only monitoring vital signs such as electrocardiogram (ECG), blood pressure and oxygen saturation, but also aspects like pain, sedation, anxiety, stress, delirium, sleep quality and physical and cognitive mobilization. This advanced vision of Philips means future investigations need to include clinical research, healthcare economics, medical device technology, hospitals and health policy.

Zusammenfassung

Philips legt den Schwerpunkt bei seinen technischen Innovationen auf patientenorientierte Ergebnisse. Die Vision ist die Bereitstellung einer patientenorientierten Pflege durch Schaffung einer Umgebung, die keinen Stress oder Angst beim Patienten hervorruft und die höchstmögliche Lebensqualität nach der Entlassung aus dem Krankenhaus ermöglicht. Dies berücksichtigt nicht nur die Überwachung von Vitalparametern wie beispielsweise Elektrokardiogramm (EKG), Blutdruck und Sauerstoffsättigung, sondern auch Parameter wie Schmerz, Sedierung, Angst, Stress, Delir, Schlafqualität und körperliche und kognitive Mobilisierung. Diese zukunftsweisende Vision von Philips bedeutet, dass zukünftige Untersuchungen klinische Forschung, Gesundheitsökonomie, medizinische Gerätetechnik, Krankenhäuser und Gesundheitspolitik einbeziehen müssen.

1. Evolution of Intensive Care

Intensive care medicine faces the challenge of ensuring the survival of patients with life-threatening illnesses or disturbances in vital body functions. At the same time, more and more attention is paid to making sure that patients enjoy the highest possible quality-of-life after being discharged from the hospital. This shift has prompted the further development of intensive care guidelines. For example, Germany's evidence-based S3-DAS guideline *Management of Analgesia, Sedation and Delirium in Intensive Care Medicine*, revised in 2015, states that "the critically ill patient should be awake and alert, without pain, anxiety, or delirium to be able to actively participate in their treatment and recovery". It implies that patients are only sedated if there is a medical necessity. Thus, patients are able to perceive their environment and are more consciously aware of their medical care. It also facilitates the early mobilization and cognitive activation of patients. The result is an acceleration of the healing process and the avoidance of possible long-term physical and cognitive impairments as a consequence of the intensive therapy.

2. Philips' Vision for Intensive Care of the Future

Philips has developed a vision for intensive care of the future that accommodates this paradigm shift. Our goal is to create an optimal care journey and environment with technology-enabled patient-centered solutions that allow physicians, nurses, physiotherapists, psychologists and patients to work together towards the recovery of the patient in a cooperative and outcome-oriented manner.

3. Placing the Patient in the Center

The core idea is to focus on the well-being of the patient and give all caregivers a comprehensive and holistic view of their patients. Patients should not be reduced down to only their medical data, like vital signs and lab results, but should be regarded as people with their own living conditions and goals. A better insight into the human being behind the patient can help physicians and nurses make better decisions and determine the right therapy targets in conjunction with the patient. The ultimate goal of intensive care is to ensure the patient has a livable life. Most importantly, neither the patient nor any family members should develop so-called post-intensive care syndrome, which is a frequent complication at the present.

4. 'Cure and Care'

When patients are transferred to the Intensive Care Unit (ICU), initial focus is placed on saving their life and stabilizing them. At this stage, life-sustaining measures and the continuous monitoring of vital signs are essential. If the condition of the patient improves in the course of the intensive therapy, the self-healing powers of the patient can be activated early on in the ICU by minimizing, to the greatest extent possible, any factors prohibiting their convalescence and ensuring that conditions are in place to support their recovery.

In order to create room for maneuver so that physicians and nursing staff can dedicate more time to caring for their patients, intelligent solutions are needed that improve workflow and reduce workloads.

5. Holistic 360° View of Patients

Figure 1 illustrates the concept of a holistic 360° 'cure and care' view of the patient: We envision that the 'cure' view (shown in blue) provides intensivists with an overview of the state of the patient's various organ systems. Vital signs, such as electrocardiogram (ECG), blood pressure, oxygen saturation and heart rate, are important indicators for the cardiovascular system. In order to obtain a more complete picture, we suggest incorporating more 'care' aspects (shown in green) that are also very relevant for the patient's recovery. This includes, for example, information about whether the patient suffers from pain, anxiety, stress, or delirium, indications of sleep quality, whether and how deeply the patient is sedated, the degree of physical and cognitive mobilization, etc.

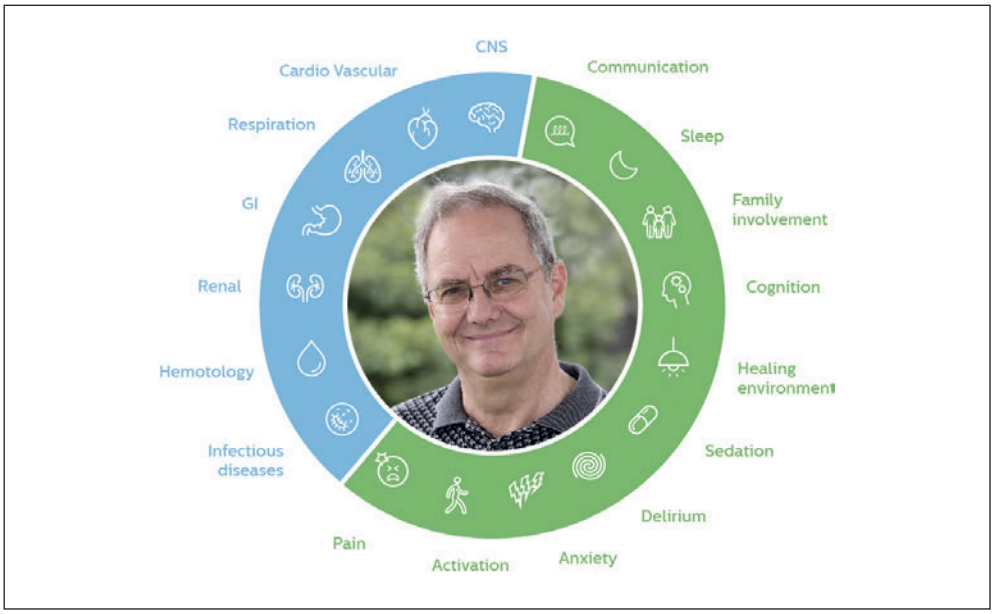

Fig. 1 Holistic 360° view of the patient

6. Measurement and Monitoring of Patient-Centered Care Parameters

While the vital signs of patients, such as ECG, blood pressure and oxygen saturation, are continuously monitored in ICUs, many other aspects that are also important for the healing process, such as pain, stress, anxiety, delirium, and sleep quality, are often taken less into consideration so far. This is due to a lack of ways to measure these parameters in an automated way. Some promising research approaches are currently emerging. Examples include the use of cameras to detect delirium by observing motoric alterations, and measuring sleep quality using only a few electroencephalogram (EEG) electrodes.

7. Patient-Centered Clinical Decision Support Systems

For the first time an innovative dashboard provides ICU physicians and nursing staff with a comprehensive holistic overview of all patients in a graphical form. At a glance, a real-time patient chart clearly indicates which parameters are noteworthy based on their absolute value or trend and therefore demand attention. Behind the scenes, intelligent, early warning systems are able to recognize when a patient's condition starts to worsen. This gives intensivists an early warning signal and enables them to take countermeasures before the patient deteriorates. Algorithms are able to predict early on if acute kidney injury, acute respiratory distress syndrome, and hemodynamic instabilities are present.

From the general overview of the ward, the physician can also zoom in on a single patient to obtain a complete and integrated overview of all data and clinical decisions pertaining to

that patient. All of the patient's information, scattered across the hospital's many IT systems, is compiled and displayed in a uniform and structured manner.

8. Support for Shift Handovers and Patient Transfers

In order to optimally support ICU personnel and to avoid errors during shift changeovers and when transferring the patient to another ward, all information relevant to the transfer is clearly displayed in the handover tool. In addition, digital dynamic checklists ensure that crucial data and scheduled activities do not get overlooked in the often hectic environment of an intensive care unit.

9. Easing Patient Mobilization

Many medical devices currently employed in the intensive care unit have been designed based on the assumption that patients spend most of their time in bed. New system concepts – such as tiny wireless, body-worn sensors for measuring vital signs, as well as smaller and more mobile patient monitors and ventilators – considerably reduce the burden placed on nursing staff to mobilize patients at an early stage.

10. Creating a Healing Environment

One important element for increasing the patient's well-being is the creation of an environment that does not cause stress or anxiety in the patient. This includes creating a cozier atmosphere in the patient's room and banishing the scary medical equipment and beeping sounds within the patient's field of vision and hearing. Light also plays an important role. Currently patients are often exposed to too little light during the day, while at night, the room does not get dark enough because nurses need light to work. This disrupts the patient's sleep. Rethinking patient-centered healthcare design and lighting solutions is therefore necessary.

11. Clinical Light Therapy Systems

The targeted use of light can help support a patient's sleep-wake rhythm. This reduces the risk of developing delirium while increasing the patient's well-being. The prescription of tailor-made light therapy is therefore a promising element of a non-pharmacological, multicomponent intervention bundle for preventing delirium.

The Charité is currently investigating whether newly designed patient rooms that use extensive luminous ceilings promote the healing process. The luminous ceilings can also render specifically colored visual content to achieve certain effects. For example, distracting and calming nature scenes that reduce pain perception, or interactive cognitive training. Based on the patient's condition, a customized playlist can be generated and played back. Thus, the luminous ceiling, with its intelligent control algorithms, is an example of a personalized digital therapy system.

12. Mobile Flexible Ventilators with Closed Loop Control

Novel flexible ventilators can be quickly and easily switched from invasive to non-invasive ventilation. Interconnectedness with the patient monitor enables a closed loop control where vital signs, such as oxygen saturation, are taken into account by the control system of the ventilator. Intelligent algorithms can help intensivists determine the right moment to transition to non-invasive ventilation or to start the weaning process.

13. Connected Intensive Care

The outcome of intensive care medicine can be improved further by streamlining processes across the acute care continuum. This allows intensivists to be involved before patients are transferred from the emergency or the operating room to the ICU, with patient monitoring and data management systems working seamlessly together.

It is also helpful for the intensivist to know the patient's vital signs prior to becoming acutely ill so that the appropriate targets can be set for the intensive therapy. In turn, an intensivist can also play an important role in supporting the patient's transition from hospital to home care.

Connected care solutions enable data to be exchanged across the health continuum. Both intensivists and practitioners benefit from a holistic and comprehensive view of their patients.

14. Recommendations for Action

In order to implement our patient-centered vision for intensive care medicine of the future, we see a need for action in the following areas:

Clinical Research

- Studies on how patient-centered intensive care affects clinical and economic outcomes.
- Evaluation of methods that continuously measure patient-centered comfort parameters such as pain, anxiety, stress, sleep and delirium.
- Evaluation of personalized digital therapy systems to support the healing process.
- Evaluation of the therapeutic efficacy of algorithms that act in the form of visual patterns.

Healthcare Economics

- Development of healthcare economic models to describe the benefits of patient-centered intensive care with respect to short- and long-term outcomes.

Medical Device Technology

- Optimization of medical devices to better support patient-centered intensive care.
- Development of methods that continuously measure patient-centered comfort parameters such as pain, anxiety, stress, sleep and delirium.
- Development of a platform for personalized digital therapy systems.
- Development of dedicated algorithms in the form of therapeutically effective visual patterns.

– Networking of medical devices across the intensive care continuum.
– Development of predictive algorithms to support clinical decisions.
– Development of cloud-based systems to exchange and process patient data across the health continuum.
– Support for hospitals to successfully implement a transition to patient-centered intensive care medicine.

Hospitals

– Re-design of intensive care units to enable patient-centered intensive care.
– Early involvement of multidisciplinary teams in the design of patient-centered intensive care units and patient rooms for new-build and modernization projects.
– Adaption of the hospital processes in the intensive care unit to the needs of patient-centered intensive care medicine and the development of an implementation strategy.
– Implementation of delirium screening and multicomponent intervention bundles to prevent delirium.
– Investments in clinical light therapy systems.
– Determined implementation of non-invasive ventilation strategies.
– Investments in patient-centered medical device technology.

Health Policy

– Promotion of research and teaching in the field of patient-centered intensive care.
– Promotion of construction measures for patient-centered ICUs.
– Promotion of investments in patient-centered medical device technology.
– Definition of criteria for measuring and rewarding the outcome of quality improvements in intensive care medicine.
– Introduction of patient satisfaction as a quality indicator.
– Adaptation and harmonization of privacy legislation to simplify the storage and processing of big anonymized patient data.

Thomas Falck
Philips Research
5656 AE Eindhoven
The Netherlands
Tel.: +31 6 15900614
E-Mail: thomas.falck@philips.com

Jacco Eerden
Philips Design
5656 AE Eindhoven
The Netherlands
Tel.: +31 6 15585016
E-Mail: jacco.eerden@philips.com

Gaby Meekes
Philips VitalMinds
5656 AE Eindhoven
The Netherlands
Tel.: +31 6 22392623
E-Mail: gaby.meekes@philips.com

Nova Acta Leopoldina NF Nr. *421*, 149–150 (2018)

Towards a Connected Intensive Care Unit (ReActive Robotics GmbH)

Alexander König (Munich)

Abstract

Increasing financial pressure forces hospitals to become more and more cost efficient. Reactive Robotics therefore focuses on early mobility, automated data collection and machine learning which results in individualized care that improves patient-centered outcomes and shortens hospital stays. It emphasizes individualized, patient-centered care to improve recovery speeds and decrease secondary complications. Unfortunately, implementation of this advanced health-care technique in clinical routine is still far off and requires a great deal of investigation.

Zusammenfassung

Wachsender finanzieller Druck zwingt Krankenhäuser dazu, immer kosteneffizienter zu werden. *Reactive Robotics* konzentriert sich daher auf Frühmobilisierung, automatisches Erfassen von Patientendaten und maschinelles Lernen, was zu individualisierter Pflege führt, die patientenorientierte Ergebnisse verbessert und Krankenhausaufenthalte verkürzen kann. Sie stellt individualisierte, patientenorientierte Pflege in den Vordergrund, um Genesungszeiten zu verbessern und Sekundärkomplikationen zu verringern. Leider ist die Umsetzung dieser zukunftsweisenden Gesundheitstechnik in den Klinikalltag noch nicht flächendeckend implementiert.

Increasing financial pressure forces hospitals to become more and more cost efficient. At the same time, new scientific innovations and the need for better patient outcomes have led to a steady rise in the standard of care. As new procedures and devices enter the market, their initial impact is to raise the cost per treatment. Two ways to decrease costs in such a market are to increase the efficacy of caregiving and to speed up recovery. Reactive Robotics' implementation of early mobility is one example of a pathway towards improved outcomes and shorter hospital stays.

We regard personalized, patient-centered provision of care as a way to improve recovery speeds and decrease the frequency of secondary complications. A patient that recovers faster incurs fewer costs.

In order to provide each patient with individually optimized treatment and the shortest path towards recovery, we believe there is great potential in leveraging the power of automated data collection and machine learning. The clearer the clinical picture of each individual patient, and the more versatile the treatment options, the easier it will be to structure the optimal treatment around an individual patient.

One obstacle remains the lack of large sets of structured data that permit the optimal treatment and care to be determined on an individualized patient basis. Sensors are already available that can continuously generate data on the patient's status, such as devices that monitor physiological signals (Electrocardiogram [ECG], oxygen saturation [SpO_2] and many others)

or, recently, even sensors that can sense the level of pain patients experience.[1] However, data gathered from patient sensors are just one step towards individualized, patient-centered care, as they only report data on the status of the patient along one specific dimension.

To help automatically generate treatment data, we propose leveraging what we call actuators, active devices that provide treatment, thereby modulating the multidimensional state of the patient. Such devices have already been successfully introduced in surgery, and are now entering the Intensive Care Unit (ICU). Examples are robotic therapy devices for early mobilization (Reactive Robotics[2]), automatic service trolleys[3] that automatically record the consumables required per patient, or some initial approaches towards individualized virtual-reality treatment systems (Charité's ICU of the future, see Luetz et al. 2016).

While many concept devices are in the development pipeline, work still needs to be done to make lab concepts fit for the real world. A technological solution that makes the work of a caregiver more complicated rather than easier will not find broad acceptance. One example from our own experience is the introduction of robotics for early mobilization in the ICU. Although concepts have long been available, mastering the complexity of ensuring that lines, ventilators and monitors remain continuously connected, and organizing life-support during therapy times is still a challenge. With staff focusing on ensuring the safety of their patients and a continuous supply of oxygen during therapy, it is hard for them to focus on customizing the treatment around the individual needs of the patient.

Once a connected set of sensors and treatment devices (or actuators) are available, these devices will need to be able to jointly collect data. When combined with data from patient monitors plus additional patient data, these machines will allow larger datasets to be generated that can potentially offer more and more individualized treatment. With the help of machine learning, clinicians will be able to learn how to individualize the treatment intervention. Data collection will need to be more automated so that caregivers are not forced to fill in databases.

Our call for action therefore focuses on industrializing available concepts so they experience wide-spread dissemination in ICUs. In the short run, interventions such as early mobility will decrease health care costs. In the long run, the collection of integrated ICU data will decrease costs and improve outcomes. Our vision is to have a large body of data available to caregivers to curate therapies around individualize patient needs. We foresee a future of patient-centered, individualize caregiving that alleviates clinical staff from the physically burdensome work so they can focus their attention on the individual.

References

Luetz, A., Piazena, Weiss, B., Finke, A., Willemeit, T., and Spies, C.: Patient-centered lighting environments to improve health care in the intensive care unit. Clin. Health Promot. *6*, 5–12 (2016)

Dr. Alexander König
Reactive Robotics GmbH
Landsberger Straße 234
80687 Munich
Germany

Tel.: +49 89 54636278
E-Mail: info@reactive-robotics.com

1 www.dolorsys.de.
2 www.reactive-robotics.com.
3 https://www.iml.fraunhofer.de/en/fields_of_activity/health_care_logistics_en/hospital_logistics.html.

Nova Acta Leopoldina NF Nr. *421*, 151–156 (2018)

Point-of-Care Testing of the Serum Cholinesterase Activity. A Novel Early Indicator of the Systemic Inflammation or Yet Another Vague Sepsis Biomarker? (Dr. F. Köhler Chemie GmbH)

Aleksandar R. Zivkovic,[1] Karsten Schmidt[1] and Stefan Hofer[1,2]

Abstract

Butyrylcholinesterase (BChE) is a promising biomarker that enables the early diagnosis of emerging systemic inflammation. Early measurements using a Point-of-Care Testing (POCT) system should improve patient outcomes. Cooperation between industry and science is necessary to further study the best diagnostic and treatment options so that the scientific results can be implemented in clinical routines, thereby improving patient-centered outcomes.

Zusammenfassung

Butyrylcholinesterase (BChE) ist ein zukunftsträchtiger Biomarker, der die frühzeitige Diagnose einer aufkommenden systemischen Entzündung ermöglicht. Frühzeitige Messungen durch die patientennahe Sofortdiagnostik sollen Patientenergebnisse verbessern. Die Zusammenarbeit zwischen Industrie und Wissenschaft ist notwendig, um die besten Diagnose- und Behandlungsmöglichkeiten weiter zu untersuchen, so dass die wissenschaftlichen Erkenntnisse in den Klinikalltag umgesetzt werden können und somit die patientenorientierten Resultate verbessern.

Early diagnosis of systemic inflammatory response syndrome (SIRS) is fundamentally important for effective therapy in modern intensive care medicine. Fast and accurate diagnosis of systemic inflammation plays a pivotal role in critical care therapy (Rivers et al. 2001). Indeed, early goal-directed therapy provided in the Intensive Care Unit (ICU) in the first 6 h following disease presentation has been shown to reduce mortality by 16 % over standard care (Rivers et al. 2012).

Systemic inflammation is a general response to noxious stimuli mediated by the activation of the innate immune system (Rock et al. 2010). An effective immunological reaction relies on a balanced interplay between pro- and anti-inflammatory mechanisms (Matzinger 1994, Bone et al. 1997). The pathogenesis of systemic inflammation, induced by external pathogens, is closely related to sepsis and is not fully understood. With high mortality rates (25 – 38 %), it remains a challenge in the ICU (Annane et al. 2003, Angus et al 2001). Trauma-induced sterile inflammation is a complex and dynamic process often giving rise to severe consequences when inadequately treated. More than 170 inflammation biomarkers have been described in the literature and proposed as a way to predict or diagnose systemic inflammation (Pierrakos and Vincent 2010). However, no definitive diagnostic tool for the early detection of systemic inflammation has yet been identified. A combination of laboratory

1 Department of Anesthesiology, Heidelberg University Hospital, Heidelberg, Germany.
2 Clinic for Anesthesiology, Intensive Care and Emergency Medicine I, Westpfalz Hospital, Kaiserslautern, Germany.

tests, clinical signs, and patient history records are used in the process of diagnosing systemic inflammation.

Cholinergic neurotransmission has been shown to play an important role in the regulation of the immune response during inflammation. Increased vagus nerve activity during inflammation inhibits peripheral cytokine release through a mechanism that requires nicotinic acetylcholine receptors (Wang et al. 2003). The information from peripheral inflammatory responses is gathered through afferent fibers of the vagus nerve, followed by an instant efferent feedback in a homeostatic fashion (Tracey 2002). This mechanism has been described as the "cholinergic anti-inflammatory pathway". Indeed, previous studies have suggested that administering the cholinesterase inhibitor physostigmine (Anticholium®) to activate the cholinergic anti-inflammatory pathway during experimental endotoxemia might prove beneficial in treating systemic inflammation (Hofer et al. 2008, Peter et al. 2010). Cholinergic activation can modulate the immune response to limit pro-inflammatory processes to a non-toxic range. The stimulated vagus nerve releases acetylcholine, which inhibits macrophage activation and the release of pro-inflammatory cytokines, and simultaneously promotes the synthesis and secretion of anti-inflammatory cytokines, thereby attenuating the development of endotoxic shock in rats (Borovikova et al. 2000). However, the clinical implications of cholinergic activity during the immune response has yet to be evaluated.

Serum cholinesterase, termed "butyrylcholinesterase" (BChE), is an enzyme that hydrolyzes the neurotransmitter acetylcholine. BChE is a nonspecific choline esterase, which is abundant in the blood, liver and brain (Kaplay 1976). BChE is synthesized in the liver and has therefore been conventionally used as a liver function biomarker (Burnett 1960, Meng et al. 2013). Indeed, previous studies have suggested that BChE is an important indicator of hepatic dysfunction in sepsis (al-Kassab and Vijayakumar 1995). In addition, the role of BChE in lipid metabolism, obesity, and diabetes mellitus has been identified, however, the exact physiological function of BChE remains unknown (Iwasaki et al. 2007, Rao et al. 2007). Altered serum BChE activity might indicate disrupted acetylcholine hydrolysis, which would, in turn, indirectly signal an imbalance between the pro- and anti-inflammatory systemic responses mediated by nonneuronal cholinergic activity. Measuring BChE activity may provide an indirect estimate of the systemic response to a noxious stimulus, allowing ICU staff to promptly respond with the appropriate therapy.

We were previously able to demonstrate that patients diagnosed with severe systemic inflammation show a marked reduction in serum cholinesterase activity (Fig. 1) (Zivkovic et al. 2015). However, due to the high variability in the onset and etiology of the observed conditions, it was difficult to determine whether the change in enzyme activity correlated with the emergence of the disease.

Trauma is a sudden and initially pathogen-free inflammatory challenge that triggers a prompt immune response. Previous studies have shown that the magnitude and duration of the immune reaction correlate well with the extent of the trauma (Shih et al. 1998, Choileain and Redmond 2006). A dynamic change in serum cholinesterase activity has been reported to follow a severe traumatic injury. Serum cholinesterase continuously decreased in patients with severe polytrauma over an observation period of 7 days. The authors suggested that the observed decrease in serum cholinesterase may be regarded as a supplemental trauma severity indicator and as a prognostic patient outcome tool (Ba et al. 2014). Our recent study confirmed these findings by measuring BChE activity during the initial 6 hours following traumatic injury (Fig. 2) (Zivkovic et al. 2016).

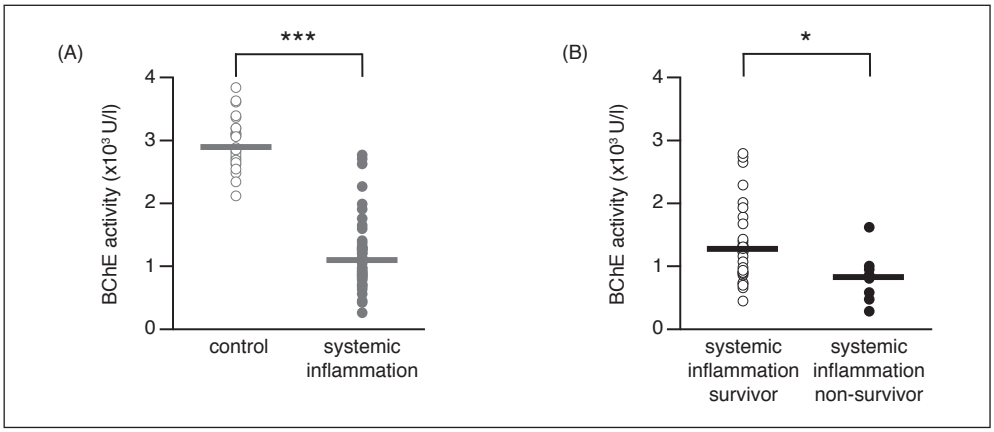

Fig. 1 Reduced BChE activity in patients with systemic inflammation. (*A*) Scatter plots represent results of BChE point-of-care testing (POCT) obtained from healthy volunteers (gray open circles, control) and patients diagnosed with systemic inflammation (gray closed circles). (*B*) Based on a subsequent 28-day survival analysis, patients were further divided into survivor and non-survivor subgroups (black open and closed circles, respective). Adapted from Zivkovic et al. 2015.

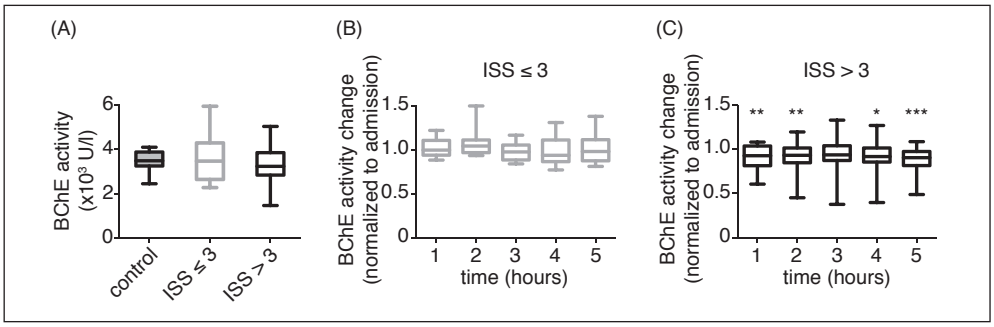

Fig. 2 Reduction in BChE activity in patients with traumatic injury. (*A*) Initial BChE activity measured at hospital admission did not differ between healthy volunteers (control, filled gray), patients with an ISS ≤ 3 (open gray), and those with ISS > 3 (black, Kruskal-Wallis test followed by Dunn's multiple comparisons test). Blood samples from patients without severe injury (ISS ≤ 3, gray, *B*) and patients with traumatic injury (ISS > 3, black, *C*) were tested for changes in BChE activity over 5 h following hospital admission. Values represent relative change in BChE activity, normalized to the initial enzyme activity recorded at admission (*A*). Box plots in panels (*A*), (*B*), and (*C*) represent medians with 25 and 75 percentiles; error bars are minimum and maximum values. *P<0.05; **P<0.01; ***P<0.001. Observed change in BChE activity has been tested for repeated measures using the Friedman test followed by Dunn's multiple comparisons test. Abbreviations: BChE, butyrylcholinesterase; ISS, injury severity score. Adapted from Zivkovic et al. 2016.

The use of point-of-care testing (POCT) in patient treatment has proven beneficial for patient security and therapy. Compared to a conventional diagnostic laboratory analysis, the time interval between the analysis and results of POCT is remarkably shorter, allowing for immediate decisions to be made about further therapeutic and diagnostic procedures. Indeed, early goal-directed therapy has proven essential in treating critically ill patients diagnosed with

severe sepsis. Using POCT to measure serum BChE activity might be beneficial for early detection of the systemic inflammatory response. A POCT device, used to determine BChE activity, uses an enzymatic assay that provides the rapid and precise determination of BChE activity in human whole blood without the need to pretreat the samples. Alternatively, after routine blood gas analysis collection, taken during the intensive care treatment as a part of the standardized ICU diagnostic and therapeutic procedure, 10 µl of blood, required for the analysis of BChE activity, could be used after completing the gas analysis.

Our recent studies provide insight into the potential value of the POCT method in determining BChE activity. This simple test provides a rapid result in contrast to the significant time delay associated with conventional laboratory analysis. Early recognition of inflammation is essential for the successful treatment of patients with suspected systemic inflammation and thus potential delays caused by laboratory testing can be avoided to ensure prompt initiation of appropriate treatment and early goal-directed therapy.

Moreover, our previous study reported that BChE activity is significantly reduced during systemic inflammation and that this reduction correlates with the severity of the disease. Although hepatic function used to be regarded as essential for BChE production, we showed that the reduced BChE activity associated with systemic inflammation occurs independently of, and is thus not caused by, any deficit in hepatic function in ICU patients. Therefore, BChE activity might play an important role in the diagnosis of the systemic inflammation regardless of the overall hepatic function.

In addition, our recent study showed that BChE activity decreases following a traumatic injury. The observed change in enzyme activity correlates with the onset of trauma, suggesting that the cholinergic activity plays an important role in the acute response to an inflammatory challenge. The POCT approach, used to assess BChE activity, might further improve the treatment of critically ill patients by minimizing time delays inherent to lengthy laboratory testing for other conventional inflammation markers. Measuring the dynamics of BChE activity using a POCT system might prove useful for the early diagnosis of the emerging systemic inflammation.

Finally, compared to the conventional laboratory tests that are used to diagnose inflammation (CRP and white blood cell count – WBCC), a change in BChE activity, indicating emerging systemic inflammation, can be detected much earlier. A reduction in BChE activity within the first 2 h after admission to the ICU might signal ongoing inflammation which is not detected by an increased blood CRP level until 24 h later. The POCT system, available at the bedside, enables high-risk patients to be identified early on, thereby allowing systemic inflammation to be more rapidly diagnosed and treated. The observed reduction in enzyme activity, apparent 1–2 h after hospital admission, makes this assay one of the earliest indicators of inflammation described so far. Measuring BChE activity using a POCT system at the bedside minimizes time delays often associated with conventional laboratory testing. This assay might prove beneficial in the early recognition of emerging inflammation, permitting the early commencement of anti-inflammatory therapy.

Our results suggest that using a POCT system to measure BChE activity during the systemic inflammation and in the initial phase of trauma care might help to identify patients at risk of an emerging inflammatory response. Early detection of reduced BChE levels and intervention during the primary therapeutic and diagnostic procedures in the emergency ward and intensive care unit should improve patient outcomes. Greater vigilance, the escalation of monitoring strategies, and the intensification of supporting therapy are a few treatment sug-

gestions for patients showing reduced BChE activity during their hospital stay. In conclusion, measuring BChE activity might prove beneficial in the recognition and early commencement of anti-inflammatory therapy, a decision particularly important in an ICU environment.

References

al-Kassab, A. S., and Vijayakumar, E.: Profile of serum cholinesterase in systemic sepsis syndrome (septic shock) in intensive care unit patients. Eur. J. Clin. Chem. Clin. Biochem. *33*/1, 11–14 (1995)

Angus, D. C., Linde-Zwirble, W. T., Lidicker, J., Clermont, G., Carcillo, J., and Pinsky, M. R.: Epidemiology of severe sepsis in the United States: analysis of incidence, outcome, and associated costs of care. Crit. Care Med. *29*/7, 1303–1310 (2001)

Annane, D., Aegerter, P., Jars-Guincestre, M. C., and Guidet, B.: Current epidemiology of septic shock: the CUB-Réa network. Amer. J. Respir. Crit. Care Med. *168*/2, 165–172 (2003)

Ba, L., Wu, D., Qian, A., Zhang, M., and Xiong, B.: Dynamic changes of serum cholinesterase activity after severe trauma. J. Zhejiang Univ. Sci. B. *15*, 1023–1031 (2014)

Bone, R. C., Grodzin, C. J., and Balk, R. A.: Sepsis: a new hypothesis for pathogenesis of the disease process. Chest. *112*, 235–243 (1997)

Borovikova, L., Ivanova, S., Zhang, M., Yang, H., Botchkina, G. I., Watkins, L. R., Wang, H., Abumrad, N., Eaton, J. W., and Tracey, K. J.: Vagus nerve stimulation attenuates the systemic inflammatory response to endotoxin. Nature *405*, 458–462 (2000)

Burnett, W.: An assessment of the value of serum cholinesterase as a liver function test and in the diagnosis of jaundice. Gut *1*/4, 294–302 (1960)

Choileain, N., and Redmond, P.: Cell response to surgery. Arch. Surg. *141*, 1132–1140 (2006)

Hofer, S., Eisenbach, C., Lukic, I. K., Schneider, L., Bode, K., Brueckmann, M., Mautner, S., Wente, M. N., Encke, J., Werner, J., Dalpke, A. H., Stremmel, W., Nawroth, P. P., Martin, E., Krammer, P. H., Bierhaus, A., and Weigand, M. A.: Pharmacologic cholinesterase inhibition improves survival in experimental sepsis. Crit. Care Med. *36*/2, 404–408 (2008)

Iwasaki, T., Yoneda, M., Nakajima, A., and Terauchi, Y.: Serum butyrylcholinesterase is strongly associated with adiposity, the serum lipid profile and insulin resistance. Intern. Med. *46*/19, 1633–1639 (2007)

Kaplay, S. S.: Acetylcholinesterase and butyrylcholinesterase of developing human brain. Biol. Neonate *28*, 65–73 (1976)

Matzinger, P.: Tolerance, danger, and the extended family. Annu. Rev. Immunol. *12*, 991–1045 (1994)

Meng, F., Yin, X., Ma, X., Guo, X. D., Jin, B., and Li, H.: Assessment of the value of serum cholinesterase as a liver function test for cirrhotic patients. Biomed. Rep. *1*/2, 265–268 (2013)

Peter, C., Schmidt, K., Hofer, S., Stephan, M., Martin, E., Weigand, M. A., and Walther, A.: Effects of physostigmine on microcirculatory alterations during experimental endotoxemia. Shock *33*/4, 405–411 (2010)

Pierrakos, C., and Vincent, J. L.: Sepsis biomarkers: a review. Crit. Care *14*/1, R15 (2010)

Rao, A. A., Sridhar, G. R., and Das, U. N.: Elevated butyrylcholinesterase and acetylcholinesterase may predict the development of type 2 diabetes mellitus and Alzheimer's disease. Med. Hypotheses *69*/6, 1272–1276 (2007)

Rivers, E. P., Katranji, M., Jaehne, K. A., Brown, S., Abou Dagher, G., Cannon, C., and Coba, V.: Early interventions in severe sepsis and septic shock: a review of the evidence one decade later. Minerva Anesthesiol. *78*, 712–724 (2012)

Rivers, E., Nguyen, B., Havstad, S., Ressler, J., Muzzin, A., Knoblich, B., Peterson, E., Tomlanovich, M., and *Early Goal-Directed Therapy Collaborative Group*: Early goal-directed therapy in the treatment of severe sepsis and septic shock. New Engl. J. Med. *345*, 1368–1377 (2001)

Rock, K., Latz, E., Ontiveros, F., and Kono, H.: The sterile inflammatory response. Annu. Rev. Immunol. *28*, 321–342 (2010)

Shih, H. C., Su, C. H., and Lee, C. H.: Alternations of surface antigens on leukocytes after severe injury: correlation with infectious complications. Intensive Care Med. *24*, 152–156 (1998)

Tracey, K. J.: The inflammatory reflex. Nature *420*/6917, 853–859 (2002)

Wang, H., Yu, M., Ochani, M., Amella, C. A., Tanovic, M., Susarla, S., Li, J. H., Wang, H., Yang, H., Ulloa, L., Al-Abed, Y., Czura, C. J., and Tracey, K. J.: Nicotinic acetylcholine receptor alpha7 subunit is an essential regulator of inflammation. Nature *421*/6921, 384–388 (2003)

Zivkovic, A., Bender, J., Brenner, T., Hofer, S., and Schmidt, K.: Reduced butyrylcholinesterase activity is an early indicator of trauma-induced acute systemic inflammatory response. J. Inflamm. Res. *9*, 221–230 (2016)

Zivkovic, A. R., Schmidt, K., Sigl, A., Decker, S. O., Brenner, T., and Hofer, S.: Reduced serum butyrylcholinesterase activity indicates severe systemic inflammation in critically ill patients. Mediators Inflamm. *2015*, 27460 (2015)

Dr. Aleksandar R. Zivkovic
Department of Anesthesiology
Heidelberg University Hospital
Im Neuenheimer Feld 110
69120 Heidelberg
Germany
E-Mail: aleksandar.zivkovic@med.uni-heidelberg.de

Dr. Karsten Schmidt
Department of Anesthesiology
Heidelberg University Hospital
Im Neuenheimer Feld 110
69120 Heidelberg
Germany
E-Mail: Karsten.Schmidt@med.uni-heidelberg.de

Prof. Dr. Stefan Hofer
Clinic for Anesthesiology
Intensive Care and Emergency Medicine I
Westpfalz Hospital
Hellmut-Hartert-Straße 1
67655 Kaiserslautern
Germany
Tel.: +49 631 202031030
Fax: +49 631 202031922
E-Mail: shofer@westpfalz-klinikum.de

Nova Acta Leopoldina NF Nr. *421*, 157–160 (2018)

CytoSorb® to Counteract Excessive Hyperinflammation in Intensive Care Unit Patients (CytoSorbents Europe GmbH)

Jörg Scheier (Berlin)

Abstract

A high proportion of Intensive Care Unit (ICU) patients suffer from long-term consequences, however, the underlying pathophysiological mechanisms are widely unknown. CytoSorbents focuses on hyperinflammation as the primary cause for short- and long-term impairment and has therefore developed CytoSorb® to counteract excessive hyperinflammation in ICU patients during the acute phase of many diseases.

Zusammenfassung

Ein großer Teil der Intensivpatienten leidet an Langzeitfolgen, aber die zugrundeliegenden pathophysiologischen Mechanismen sind weitgehend unbekannt. CytoSorbents richtet den Fokus auf überschießende systemische Entzündungsreaktionen als der Hauptursache für Kurz- und Langzeitschäden und hat daher CytoSorb® entwickelt, um einer übermäßigen Hyperinflammation bei Intensivpatienten während der akuten Phase vieler Erkrankungen entgegenzuwirken.

Tremendous progress has been made in recent decades in treating critically ill patients thanks to innovative medical device therapies and new pharmaceutical approaches in modern intensive care medicine. This has considerably increased a patient's chance of surviving life-threatening illnesses after treatment in the Intensive Care Unit (ICU). Many of these acute illnesses are accompanied by dysfunction or failure of various organ systems, often culminating in "multi-organ failure", a condition which frequently requires extensive artificial organ support or replacement. Today it is still associated with an extremely high mortality rate ranging from 50 % to 100 %. Although short-term survival rates (i.e. survival of ICU and hospital stay) have increased considerably with advances in modern intensive care medicine, the impact of this progress on the long-term outcomes and quality of life (QoL) of these patients after discharge from the ICU and hospital largely remains unclear and insufficiently investigated. It is well known that a high proportion of patients who have undergone long, complex and invasive ICU treatments suffer from long-term consequences, such as polyneuropathy, psychiatric disorders and chronic kidney failure. These can potentially prevent patients from returning to their previous daily routines and to the workplace. Not only is the QoL of the affected patients considerably restricted, there are also economic consequences such as costs for long-term medical treatment and the inability to work.

The pathophysiological mechanisms that lead to these long-term sequelae after ICU survival are widely unknown. Currently the primary focus of ICU therapy during the acute phase of the patient's illness is to provide immediate technical support or to replace acutely

failing organ systems. This often involves complex and invasive technical measures such as extracorporeal membrane oxygenation (ECMO), continuous renal replacement therapy (CRRT) and long-term mechanical ventilation. While such advanced therapeutic measures are becoming increasingly successful in terms of acute-phase survival, there is much less focus on how they impact the patient's ongoing care and QoL after ICU survival and hospital discharge; the related impact of duration and invasiveness of the therapeutic measures taken during the ICU stay have remained largely uninvestigated. The underlying pathophysiological mechanisms responsible for the well-known, persistent physical and psychiatric disorders are not yet fully understood. However, it seems plausible that long-lasting states of critical disease with multiple organ failure (where survival would have been completely impossible just a few years ago), are likely to have a long-term impact on organ function and body homeostasis in general.

Today it is well accepted that acute, dysregulated systemic hyperinflammatory syndrome, a host response to infectious or non-infectious noxae, plays a major role in the development of organ dysfunction and ultimately multi-organ failure in many states of critical disease. Such an overshooting systemic inflammatory response can be triggered by a multitude of conditions, including bacterial, viral or fungal infections, as well as non-infectious sources of inflammation, such as pancreatitis, burns or major surgery e.g. cardiac. Inflammatory reactions basically serve as a defense mechanism within the area of the initial damage or infection, but can easily get out of physiological control, spread systemically, and then negatively impact even initially non-affected organs throughout the body, resulting in organ dysfunction and ultimately multi-organ failure. It can reasonably be assumed that residual states of such systemic hyperinflammatory processes during ICU treatment could play a role in the development of long-term complications, possibly along with persisting chronic inflammation phenomena.

The extent to which the severity and duration of such critical disease states and variables (i.e. duration and invasiveness of ventilation, circulatory support, kidney and liver support systems, number and invasiveness of surgical procedures and other therapies) affect outcomes beyond ICU and hospital survival is still unknown. It has therefore been difficult to define strategies to mitigate the risk of long-term deleterious effects, despite the fact that, in most cases, no alternative treatment options are available during the acute phase anyway.

Without questioning the value of the outstanding advances in life-saving ICU treatments, it seems appropriate to focus on more than just ICU survival by keeping an eye on the long-term fate of these patients.

Even if it is not completely clear what the optimal approach for improving long-term outcomes would be, a strategy that aims to reduce the length of ICU stay, accelerate recovery of physiologic organ functions and consequently lower the need for invasive organ support could potentially decrease the severity of long-term complications and increase the QoL of ICU survivors. As outlined above, most organ failures requiring artificial support or replacement are caused and maintained by acute, out-of-control systemic hyperinflammatory processes. These are characterized by an overshooting and systemic release of inflammatory mediators such as cytokines and chemokines, which leads to capillary leakage, vasodilation, impairment of organ perfusion on the microcirculatory level, and, consequently, to a lack of tissue oxygen supply. This ultimately results in profound states of shock and organ failure.

In the light of this fact, there is potential promise in pursuing a therapeutic approach during the acute phase of ICU treatment aimed at modulating and reducing such overshooting

systemic hyperinflammatory phenomena to more physiologic levels. The goal would not only be to increase the chances of ICU survival, but also to reduce the likelihood of persisting residual states of these processes, and possibly also to prevent the occurrence of chronic states of inflammation.

Recently a novel medical device concept for treating acute hyperinflammatory states of various origins was introduced to critical care medicine (CytoSorb®, CytoSorbents Corp., Monmouth Junction, NJ, USA). The primary purpose of this concept is to counteract the excessive hyperinflammation in ICU patients during the acute phase of many diseases. This would help to increase the chance of surviving the extremely critical, life-threatening phase of multi-organ dysfunction and acute instability. However, the related effects leading to improvement in short-term survival may also exert a positive effect on the long-term outcome and QoL after an ICU stay. The acute effects of this immunomodulatory therapy lead to quicker restoration of tissue oxygen supply, thereby shortening the periods of organ dysfunction and failure. This, in turn, reduces the need for invasive artificial organ support measures and may potentially shorten overall ICU stays, which may – though yet to be investigated – affect the mitigation of long-term chronic inflammation and the related negative effects this has on the patient's wellbeing. The exact effects still need to be established, but it seems highly likely that this novel concept could have the potential to improve QoL and long-term outcomes after ICU survival. Another interesting consequence is the potential to save costs by reducing the need for treatment of residual states. Other possibilities include quicker and better re-integration into daily life and a return to work, again with considerable savings in associated costs.

The CytoSorb technology consists of a 300 ml cartridge, filled with numerous small, highly bio- and hemocompatible polymer beads, capable of removing hydrophobic molecules up to approximately 60 kDa in size from the bloodstream through physicochemical adsorption. This is the size of most substances that are involved in acute hyperinflammatory reactions and also includes a variety of other, harmful substances such as myoglobin, bilirubin, free hemoglobin and a number of bacterial toxins. The cartridge is designed for integration into virtually any extracorporeal blood circuit used in critical care medicine, such as continuous or intermittent renal replacement therapies or extracorporeal membrane oxygenation (ECMO). The main therapeutic effect is to attenuate dysregulated, hyperinflammatory response syndromes (often called "cytokine storm") present in sepsis and also many non-infectious disease states, by reducing elevated levels of circulating cytokines and other inflammatory mediators. This modulation and dampening of the immune response can lead to an improvement in hemodynamics, a reduction in the need for vasopressors and, by improved restoration of tissue oxygen supply on the microcirculatory level, an overall increase in the chance for recovery of organ function and a shortening of invasive organ-supportive therapies. The therapy has shown promising clinical results in a wide variety of hyperinflammatory states after e.g. cardiac surgery, cardiogenic shock, trauma, burns, pancreatitis and, as a major indication today, in sepsis and septic shock. So far it has been used safely in more than 20,000 single treatments in more than 11,000 patients worldwide without any reported adverse side effects related to the device.

Today this therapeutic concept is primarily used during the acute phase to stabilize and recover organ function. It has resulted in the improvement of short-term outcomes and survival rates, however, future application fields are multi-fold and have yet to be explored.

The awareness of the medical community about the crucial role of acute and chronic inflammation processes (including but not limited to autoimmune diseases and oncology) is

in its infancy, and one can expect that a vast array of potential applications for inflammation-mediating therapies will emerge and be investigated within the framework of scientific studies. In this context, such an immunomodulating strategy during an ICU stay is expected to potentially have a positive impact on the long-term outcome and quality of life of many critically ill patients and should be considered a major scientific field of interest.

Dr. Jörg Scheier
Senior Medical Director Europe
CytoSorbents Europe GmbH
Müggelseedamm 131
12587 Berlin
Germany
E-Mail: support@cytosorbents.com

Strategies to Achieve Patient-Centered-Outcomes

Nova Acta Leopoldina NF Nr. *421*, 163–167 (2018)

Gaps and Evidence

Claudia Spies ML, Gunnar Lachmann and Michael Schäfer
(Berlin)

Abstract

Patient-related outcomes are recommended to be the main focus of Intensive Care Unit (ICU) treatment. Post-intensive care syndrome (PICS) is seen in more than 50 % of the ICU patients and comprises cognition, mobility and psychosocial impairment. In the past basic research has failed with its introduction of numerous experimental models to represent relevant primary or secondary outcome parameters in clinical science. For all ICU studies, a long-term follow-up of all included ICU patients should be encouraged after ICU discharge for at least one year to report quality of life in the domains cognition, mobility and psychosocial outcome. Feedback to ICU medical teams is urgently required to enhance awareness for patient-centered outcomes beyond ICU and in-hospital mortality.

Zusammenfassung

Patienten-orientierte Heilungserfolge werden als der Schwerpunkt der Behandlung in Intensivstationen betrachtet. Das Postintensive Behandlungssyndrom (PICS) zeigt sich bei mehr als 50 % der Intensivpatienten und umfasst Beeinträchtigungen in Kognition, Mobilität und im psychosozialen Bereich. In der Vergangenheit ist es der Grundlagenforschung nicht gelungen, die Einführung verschiedener experimenteller Modelle, die primäre und sekundäre Behandlungsresultate widerspiegeln, in der klinischen Forschung ausreichend zu sichern. Für alle Intensivpatienten sollte zumindest für ein Jahr nach der Entlassung aus der Intensivstation eine Langzeit-Nachkontrolle erfolgen, um die Lebensqualität in den Bereichen Kognition und Mobilität sowie psychosoziale Einschränkungen festzuhalten. Das entsprechende Feedback für das Personal der Intensivstationen ist erforderlich, um das Bewusstsein für Patienten-orientierte Behandlungsresultate über die Intensivstationen- und die Krankhaussterblichkeit hinaus zu fördern.

1. Gaps Awaiting Solutions

Patient-related outcomes are recommended to be the main focus of Intensive Care Unit (ICU) treatment. Post-intensive care syndrome (PICS) is seen in more than 50 % of the ICU patients and comprises cognition, mobility and psychosocial impairment. PICS is often the result of eminence-based instead of evidence-based medicine and has long-term devastating sequelae for ICU patients and their relatives such as dementia, immobility and anxiety disorders (Davidson and Stutzer 2016). Still without an adequate answer is previous research, too often related to resource allocation such as ventilator days or ICU length of stay, considering more high-end techniques and short-term economic considerations. The more the patient is ventilated the more the in-patient and out-patient reimbursement. This is not the way patients want us to perform ICU treatment. Therefore, stakeholders involved in ICU treatment are recommended to cooperate closely to avoid PICS. Since health-care industry is a major column

of economy,[1] numerous stakeholders involved in medicine these days are to be considered besides the typical stakeholders comprising the core medical team (e.g. physicians, nurses, physiotherapists). Due to the fact that industry and core medical teams cooperate too late in the process often ICU developments are not carried out in accordance with the respective standard on a best estimate basis and are not continually revalued and based on patient-centered outcomes. It should be in the focus of politicians to guarantee an adequate available evidence-based quality and to offer to remit payment of taxes to those companies or to reimburse those institutions only who consent to cooperate in the sense of the patients and their relatives.

Adequate quality is considered if PICS is avoided, i.e.:

- Implemented quality indicators (DIVI standard; Braun et al. 2013).
- Implemented intersectoral quality indicators (Bea@home; Kastrup et al. 2017; WeanCert, DGAICert).
- Reported long-term outcome in the quality of life domains cognition, mobility and psychosocial outcomes.

Lessons learned from Scandinavia with fewest beds but better outcomes are available patient-centered outcomes since patient history is accessable for every medical team member involved in patients' care. The *Sozialgesetzbuch* (SGB) V allows for case related administrative date including detailed information on morbidity as well as mortality to be shared with research institutions since 2012.[2] However, partial implementation of this began in 2014 and is ongoing.

2. Gaps between Basic and Clinical Science

In the past basic research has often failed with its introduction of numerous experimental models to represent relevant primary or secondary outcome parameters in clinical science. Clinical trial findings often did not match with experimental results. This is even more so with patient-centered outcomes. The strength of basic research is to identify in a well-controlled scenario principal mechanisms of disease. However, they have to be proven in the human situation and deviations from these mechanisms have to be demonstrated. Finally, it is most important that they have been shown to be able to impact patient-related and patient-centered outcomes, in particular quality of life domains.

3. Generation of Evidence

Needs assessment of research related to patient-centered outcomes in ICU settings are relevant to avoid development gaps related to business strategies not adapted to acute patient-centered care. Business usually encourages development of chronic drug and technical replacement and not acute short-term requirements because medicines and products for chronic conditions are more profitable. Pharmaceutical and engineering companies prefer to invest

1 http://www.wifor.de/presse/items/studie-belegt-oekonomische-bedeutung-der-gesundheitsindustrie-fuer-hessen.html.
2 http://dipbt.bundestag.de/extrakt/ba/WP17/378/37831.html.

in chronic conditions even if innovations for acute care prevent chronic conditions and refer to a better quality of life for the patients and their relatives. One devastating example is the failure of antibiotic drug development in the gram-negative spectrum: the last new release of a new gram-negative acting antibiotic drug was in 1987. A cost-benefit analysis by the Office of Health Economics in London calculated that the net present value of a new antibiotic is only about US $ 50 million, compared to approximately US $ 1 billion for a drug used to treat a neuromuscular disease (Bartlett et al. 2013). Therefore, politicians should consider economic advantages such as reduced taxes for companies involved in the development of pharmaceutical and technical equipment with respect to patient-centered outcomes. If stakeholders would evaluate innovations profitable it would decrease the gap between profit-related versus meaningful research for the patient and their relatives.

In addition, shortcomings from previous studies are inadequate methods. The methods of all studies are recommended to be reported before first patient-in in journals such as "trials". However, this will not help to improve the methods if participation of scientists in method discussions and, therefore, improved study protocols are not reimbursed. Previous reimbursement of researchers is only for publication of own preformed trials and fundraising of money to perform these studies. Therefore, gaps to be addressed are on one hand, how methodologically complex ICU studies can be improved in a collaborative way together with the available experienced research community, on the other hand, how protocol violation related to a lack of evidence-based routine clinical work increasing the confidence intervals of achievable routine results can be avoided. Protocol violations of evidence-based medicine underlying the clinical routine treatment, i.e. reporting of adherence to quality indicators in each patient protocol should be included in the patient logs. An example is delirium treatment: if patients are oversedated as it is still relevant in ICU settings, delirium (Luetz et al. 2014) might not be detected with the new DSM-5 criteria (*American Psychiatric Association 2013*) and, therefore, might not be treated in time leading to more cognitive disability even one year after ICU treatment (Pandharipande et al. 2013). Therefore, anonymized data availability and biometric reporting should include protocol violations not only from study protocols, but also from the underlying evidence based clinical pathways related quality indicators (DIVI; Braun et al. 2013, Kastrup et al. 2009).

For all ICU studies, a long-term follow-up of all included ICU patients should be encouraged after ICU discharge for at least one year as well as registry of all ICU patients not being included in studies (health-care approach) as well as reimbursement of GPs for all ICU patients to report quality of life in the domains cognition, mobility and psychosocial outcome. Feedback to ICU medical teams is urgently required to enhance awareness for patient-centered outcomes beyond ICU and in-hospital mortality.

4. Dissemination of Evidence

Dissemination of evidence is an important educational tool to understand the link between acute care and patient-centered outcomes. Often reported outcomes in meetings and conferences are mortality rates or ventilator days or ICU or hospital length of stay. Rarely, reporting of patient-centered outcomes after ICU for studies presented in meetings, conferences etc. are available. In addition, the quality of the study design often lack protocol violations within the study design and within the clinical pathways (implementation rate of quality indicators,

relevance of the achieved outcomes with respect to the included and excluded patients and the confidence intervals combining study protocols and underlying clinical routine). Despite this shortcomings, these gaps are not reported during the meetings and conferences. Physician chambers in Germany involved in rating the quality of the conferences and meetings might consider this lack of quality. Feedback report forms of the audience to the physicians' chamber might include checklists to evaluate the adequate patient-centered outcome of the presented study and might consider a reduced CME level for unreported patient-centered outcomes.

5. Implementation of Evidence

Implementation protocols with quality indicators related on patient-centered outcomes are highly recommended to be in the focus of peer-reviews organized by the physician chambers. In ICU settings, peer reviews are available organized by the physicians' chamber (Braun et al. 2010). These peer reviews can be used to evaluate regional hospitals of the federal county and give them direct feedback if patient-centered outcomes are considered to be not achieved. Peer reviews can be used to discuss, equal with the peers, on patient-centered outcomes and to exchange knowledge to improve quality of life after ICU discharge for the patients and their relatives. Peer reviews are considered an excellent tool in continuous quality improvement. Gaps detected within a hospital can be used to train medical teams as multipliers to overcome low implementation rates of evidence-based quality indicators and to sustain adequate implementation rates (Radtke et al. 2012).

Gaps to achieve the implementation goals are recommended to be addressed in yearly reports given to the different hospitals. If no peer-reviews are available, and if no quality indicators are reported, the physician chambers might consider to reduce the time approved for ICU accreditation. Health insurance companies are encouraged to reimburse quality, i.e. implemented medical society consented quality indicators and their relevance in patient-centered outcomes.

References

American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders. Fifth Edition. 2013

Bartlett, J. G., Gilbert, D. N., and Spellberg, B.: Seven ways to preserve the miracle of antibiotics. Clin. Infect. Dis. *56*/10, 1445–1450 (2013)

Braun, J. P., Bause, H., Bloos, F., Geldner, G., Kastrup, M., Kuhlen, R., Markewitz, A., Martin, J., Mende, H., Quintel, M., Steinmeier-Bauer, K., Waydhas, C., Spies, C., and *NeQuI* (Quality Network in Intensive Care Medicine): Peer reviewing critical care: a pragmatic approach to quality management. Ger. Med. Sci. *8*, Doc23 (2010)

Braun, J. P., Kumpf, O., Deja, M., Brinkmann, A., Marx, G., Bloos, F., Brinkmann, A., Marx, G., Bloos, F., Kaltwasser, A., Dubb, R., Muhl, E., Greim, C., Bause, H., Weiler, N., Chop, I, Waydhas, C., and Spies, C.: The German quality indicators in intensive care medicine 2013. Second edition. Ger. Med. Sci. *11*, Doc09 (2013)

Davidson, J. E., and Stutzer, K.: The ethics of post-intensive care syndrome. AACN Adv. Crit. Care *27*/2, 236–240 (2016)

Kastrup, M., Dossow, V. von, Seeling, M., Ahlborn, R., Tamarkin, A., Conroy, P., Boemke, W., Wernecke, K. D., and Spies, C.: Key performance indicators in intensive care medicine. A retrospective matched cohort study. J. Int. Med. Res. *37*/5, 1267–1284 (2009)

Kastrup, M. T. B., Tittmann, B., Sawatzki, T., Gersch, M., Vogt, C., Rosenthal, M., Rousseau, S., und Spies, C.: Übergang von stationärer Beatmung zur außerklinischen Beatmung: Prozessbeschreibung und Qualitätsindikatoren. German Medical Science *15*, 10–18 (2017)

Luetz, A., Balzer, F., Radtke, F. M., Jones, C., Citerio, G., Walder, B., Weiss, B., Wernecke, K. D., and Spies, C.: Delirium, sedation and analgesia in the intensive care unit: a multinational, two-part survey among intensivists. PLoS One *9*/11, e110935 (2014)

Pandharipande, P. P., Girard, T. D., Jackson, J. C., Morandi, A., Thompson, J. L., Pun, B. T., Brummel, N. E., Hughes, C. G., Vasilevskis, E. E., Shintani, A. K., Moons, K. G., Geevarghese, S. K., Canonico, A., Hopkins, R. O., Bernard, G. R., Dittus, R. S., Ely, E. W., and *BRAIN-ICU Study Investigators*: Long-term cognitive impairment after critical illness. New Engl. J. Med. *369*/14, 1306–1316 (2013)

Radtke, F. M., Heymann, A., Franck, M., Maechler, F, Drews, T., Luetz, A., Nachtigall, I., Wernecke, K. D., and Spies, C. D.: How to implement monitoring tools for sedation, pain and delirium in the intensive care unit: an experimental cohort study. Intensive Care Med. *38*/12, 1974–1981 (2012)

Prof. Dr. Claudia Spies
Dr. Gunnar Lachmann
Prof. Dr. Michael Schäfer
Department of Anesthesiology and
Operative Intensive Care Medicine
Campus Charité Mitte /
Campus Virchow-Klinikum
Charité – Universitätsmedizin Berlin
Charitéplatz 1
10117 Berlin
Germany
Tel. +49 30 450551012
Fax: +49 30 450551911
E-Mail: claudia.spies@charite.de
gunnar.lachmann@charite.de
micha.schäfer@charite.de

Scientific Symposium Abstract Winner

1st Prize: Protection from Septic Shock in Mice with Genetic Inactivation of Procalcitonin*

Johannes Keller,[1,2] Anke Jeschke,[1] Thorsten Schinke[2] and Michael Amling[2]

Objectives:
Sepsis represents the most common cause of death in non-cardiac intensive care units. Procalcitonin (PCT) is considered the most sensitive and specific marker of sepsis, however, its pathophysiological function remains unclear.

Methods:
To study a potential mediator role of PCT in experimental sepsis, mice deficient in *Calca*, the gene encoding the related proteins PCT, calcitonin (CT) and calcitonin gene-related peptide alpha (αCgrp), were challenged with intraperitoneal lipopolysaccharide (LPS) or cecal ligation and puncture (CLP). To rule out an influence of CT or αCgrp signaling, mice lacking the calcitonin receptor (CTR) or αCgrp were used as controls. Blood samples were analyzed by enzyme-linked immunosorbent assay (ELISA) whereas local events were monitored using qualitative real time polymerase chain reaction (qRT-PCR), immunohistochemistry and fluorescence-activated cell scanning (FACS) analyses. For cell culture experiments, primary macrophages were generated from bone marrow cells using macrophage colony-stimulating factor (M-CSF). Experiments involving septic mice were approved by the *Behörde für Umwelt und Gesundheit*, Hamburg.

Results and Conclusion:
Similar to humans, experimental sepsis resulted in a ubiquitous and significant induction of *Calca* expression in wild type (WT) mice. Blood analyses revealed increased levels of circulating PCT and αCgrp during septic shock, while CT levels remained normal. Mice deficient in *Calca*, representing PCT deficiency, displayed increased survival following LPS injections or CLP compared to WT littermates. In contrast, mice exclusively lacking CTR or αCgrp showed no overt phenotype during lethal endotoxemia. *In vivo*, the expression of the putative PCT receptor, calcitonin receptor-like receptor, was found predominantly in the

* A similar version of this abstract has been presented at the DKOU 2016 in Berlin.

1 Charité – Universitätsmedizin Berlin, Centrum für Muskuloskeletale Chirurgie, Berlin, Germany.
2 Universitätsklinikum Hamburg-Eppendorf, Institut für Osteologie und Biomechanik, Hamburg, Germany

lung, coinciding with reduced pulmonary macrophage influx in septic *Calca*-deficient mice. *In vitro*, PCT positively regulated the expression of pro-inflammatory cytokines including interleukin-1 and interleukin-6 in macrophages. This study provides evidence for a mediator role of PCT in septic shock with therapeutic potential for affected patients.

PD Dr. Dr. Johannes Keller
Charité – Universitätsmedizin Berlin
Campus Virchow-Klinikum
Centrum für Muskuloskeletale Chirurgie
Klinik für Unfall- und Wiederherstellungschirurgie
Augustenburger Platz 1
13353 Berlin
Germany
Tel.: +49 30 450652256
E-Mail: johannes.keller@charite.de

Prof. Dr. Michael Amling
Institut für Osteologie und Biomechanik
Universitätsklinikum Hamburg-Eppendorf
Lottestraße 59
22529 Hamburg
Germany
Tel.: +49 40 741056242
Fax: +49 40 741058010
E-Mail: osteologie@uke.de

Nova Acta Leopoldina NF Nr. *421*, 173–175 (2018)

2nd Prize: Protocol Based Physiotherapy and Muscle Activating Measures Improve Skeletal Muscle Synthesis in Intensive Care Unit acquired Weakness

Julius Grunow,[1,2] Tobias Wollersheim,[1,3] Melanie Kny,[2]
Niklas M. Carbon,[1] Moritz Giesecke,[4] Carmen Birchmeier,[3,5]
Jens Fielitz[2,3,6] and Steffen Weber-Carstens[1,3]

Background: Intensive Care Unit acquired Weakness (ICUAW) affects more than 100,000 patients every year in Germany. It is characterized by muscle weakness, muscle wasting, functional deficits, prolonged weaning from mechanical ventilation and increased mortality. Currently, no specific prevention or treatment has been established. In a clinical trial we showed that protocol based physiotherapy (pPT) alone and pPT with additional measures (adMeas) such as neuromuscular electrical stimulation, whole body vibration and the combination of both maintains larger myocyte cross-sectional area (MCSA) as opposed to standard physiotherapy (sPT) (Wollersheim et al. 2016). Muscle homeostasis is determined by a balanced myosin synthesis and degradation which play a key role in the pathophysiology of ICUAW.

Objective: The aim of the study was to investigate the impact of daily sPT, pPT and a combination of pPT and adMeas on myosin synthesis during early ICU stay.

Methods: 59 Patients at high risk for developing ICUAW (Sequential Organ Failure Assessment score ≥ 9) were included into a prospectively designed randomized controlled trial and split into multiple groups either receiving pPT (n = 11) or pPT + adMeas (n = 26). Data on patients receiving sPT (n = 22) were available from a previous trial (Wollersheim et al. 2014). Vastus lateralis muscle biopsies, surgically obtained on day 15 of critical illness, were investigated via real-time polymerase chain reaction (RT-PCR). Six muscle biopsies obtained from healthy patients undergoing elective orthopedic surgery were used to determine values

1 Charité – Universitätsmedizin Berlin, corporate member of Freie Universität Berlin, Humboldt-Universität zu Berlin, and Berlin Institute of Health – Klinik für Anästhesiologie mit Schwerpunkt operative Intensivmedizin, Berlin, Germany.
2 Experimental and Clinical Research Center (ECRC), Charité – Universitätsmedizin Berlin, Max Delbrück Center (MDC) for Molecular Medicine in the Helmholtz Association, Berlin, Germany.
3 Berlin Institute of Health (BIH), Berlin, Germany.
4 Charité – Universitätsmedizin Berlin, corporate member of Freie Universität Berlin, Humboldt-Universität zu Berlin, and Berlin Institute of Health – Centrum für Muskuloskeletale Chirurgie, Berlin, Germany.
5 Max Delbrück Centrum für molekulare Medizin (MDC) – Berlin, Germany.
6 Department of Cardiology, Heart Center Brandenburg and Medical University Brandenburg (MHB), Bernau, Germany.

for baseline mRNA expression. Non-parametric tests were performed. Ethic vote (Charité EA 2/041/10).

Results: There were no differences in baseline characteristics between the intervention groups. All ICU patients fulfilled criteria for ICUAW. Protocol based physiotherapy and pPT + adMeas increased myosin gene expression. Additional measures elicited an additive effect beyond the effect observed with pPT alone. Myosin heavy chain 1 (*MYH1*) gene expression was significantly increased with pPT + adMeas as compared to controls and patients receiving sPT. Patients treated with pPT alone showed a trend towards increased gene expression for *MYH1* when compared to the latter. Treatment with standard physiotherapy decreased gene expression for myosin heavy chain 2 (*MYH2*). The decrease in expression observed for *MYH2* is mitigated by pPT + adMeas. A trend towards compensating the reduction was observed with pPT alone. Protocol based physiotherapy in combination with additional measures increased myosin heavy chain 4 (*MYH4*) expression significantly in relation to all other treatments and while patients treated with pPT remained at baseline values, patients treated with sPT had an increase over baseline values (Fig. 1).

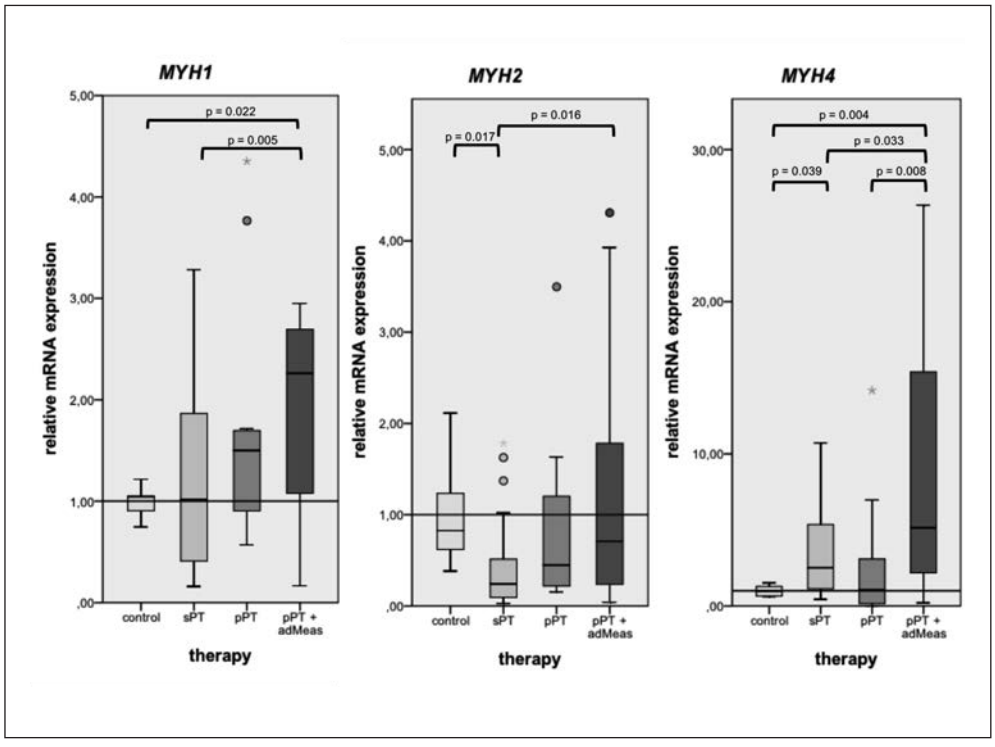

Fig. 1 Relative MYH1, MYH2 and MYH3 expression: control = healthy patients undergoing elective orthopedic surgery; sPT = standard physiotherapy; pPT = protocol based physiotherapy; pPT + adMeas = protocol based physiotherapy and additional measures.

Conclusion: Increased myosin synthesis, as indicated by increased mRNA expression in patients receiving pPT and pPT + adMeas compared to sPT and controls, matches the histological findings of greater MCSA. For the first time, we can show the beneficial effect of pPT and pPT + adMeas on maintenance of muscle mass. Identifying the exact component from the additional measures that is responsible for the observed effect requires further evaluation.

Funding: Twinning research grant (TRG-3) was given to SWC, CB and JF by the BIH. TW is participant in the clinical scientist program of Charité and BIH.

References

Wollersheim, T., Malleike, J., Haas, K., Carbon, N., Schneider, J., Birchmeier, C., Fielitz, J., Spuler, S., and Weber-Carstens, S.: ESICM LIVES 2016 – abstract A464: Randomized controlled trial using daily protocol based physiotherapy or protocol based physiotherapy with additional electrical muscle stimulation (EMS) in critically ill patients to prevent intensive care unit (ICU) acquired weakness (ICUAW). Intensive Care Med. Exp. *4*, Suppl. 1. doi: 10.1186/s40635-016-0099-9 (2016)

Wollersheim, T., Woehlecke, J., Krebs, M., Hamati, J., Lodka, D., Luther-Schroeder, A., Langhans, C., Haas, K., Radtke, T., Kleber, C., Spies, C., Labeit, S., Schuelke, M., Spuler, S., Spranger, J., Weber-Carstens, S., and Fielitz, J.: Dynamics of myosin degradation in intensive care unit-acquired weakness during severe critical illness. Intensive Care Med. *40*/4, 528–538. doi: 10.1007/s00134-014-3224-9 (2014)

Prof. Dr. Jens Fielitz
Dr. Melanie Kny
Julius Grunow
Department of Molecular Cardiology,
Experimental and Clinical Research Center (ECRC)
Charité – Universitätsmedizin Berlin
Charité Campus Buch
Lindenberger Weg 80
13125 Berlin
Germany
Tel.: +49 30 450540424/421
Fax: +49 30 450540928
E-Mail: jens.fielitz@charite.de
Melanie.Kny@charite.de
julius.grunow@charite.de

Dr. Tobias Wollersheim
Niklas M. Carbon
Prof. Dr. Steffen Weber-Carstens
Department of Anaesthesiology and
Operative Intensive Care Medicine
Charité Mitte Campus and
Virchow-Klinikum Campus
Charité – Universitätsmedizin Berlin
Augustenburger Platz 1
13353 Berlin
Germany
Tel.: +49 30 450651055
Fax: +49 30 450551909
E-Mail: tobias.wollersheim@charite.de
steffen.weber-carstens@charite.de

Dr. Moritz Giesecke
Centrum für Muskuloskeletale Chirurgie
Charité – Universitätsmedizin Berlin
Augustenburger Platz 1
13353 Berlin
Germany

Prof. Dr. Carmen Birchmeier
Developmental Biology
Max-Delbrück-Center for Molecular Medicine
Robert-Rössle-Straße 10
13092 Berlin
Germany
E-Mail: cbirch@mdc-berlin.de

3rd Prize: Muscular Glycoprotein 130 Mediates Inflammation-Induced Muscle Atrophy in Mice

Lukas Zanders,[1] Melanie Kny,[1] Erik McShane,[2] Ines Lahmann,[3] Matthias Selbach,[2,5] Carmen Birchmeier[3,5] and Jens Fielitz[1,4,5]

Background: Intensive care unit-acquired weakness (ICUAW) is a major complication of critically ill patients. ICUAW patients suffer from muscle atrophy and weakness early during the disease course. Risk factors associated with ICUAW are inflammation and sepsis (Hermans et al. 2014). The pathophysiology of muscle atrophy in ICUAW is not well understood. However, a disturbed protein homeostasis with increased degradation and decreased synthesis is involved in the disease process; but to which degree inflammation deteriorates protein homeostasis in muscle is uncertain. Recently, we reported that muscular protein degradation is activated immediately after onset of critical illness in skeletal muscle of critically ill patients and septic mice (Bierbrauer et al. 2012, Zhu et al. 2016, Wollersheim et al. 2014). We also found continuously elevated interleukin-6 (IL-6) levels in patients and mice (Langhans et al. 2014). Together, these data indicate a direct connection between inflammation and muscle atrophy.

Aim: To test the hypothesis that IL-6 via its receptor glycoprotein 130 (gp130) on myocytes mediates inflammation-induced muscle atrophy.

Methods and Results: Using a conditional *gp130* allele and a PAX7-Cre transgenic line we generated mice devoid of gp130 in the muscle cell lineage (cKO). *Gp130*$^{loxP/loxP}$ littermates without PAX7-Cre were used as controls (controls). Knockout was confirmed by quantitative real-time polymerase chain reaction (RT-PCR). At baseline, cKO showed smaller muscles as indicated by a reduction in muscle weight and myocyte cross sectional area (MCSA) of fast/type II fibers, whereas the body weight, number of satellite cells and the fiber type distribution were unaltered. To investigate the role of gp130 in inflammation-induced muscle atrophy we performed cecal ligation and puncture surgery (CLP; controls: 10, cKO: n = 15) to induce polymicrobial sepsis for 96 hours. Sham treated mice were used as controls (sham; controls: n = 6, cKO: n = 6). The survival rate did not differ between controls and cKO 96 hours after surgery.

1 Department of Molecular Cardiology, Experimental and Clinical Research Center (ECRC), Charité – Universitätsmedizin Berlin and Max Delbrück Center for Molecular Medicine in the Helmholtz Association, Berlin, Germany.
2 Proteome Dynamics, Max Delbrück Center for Molecular Medicine, Berlin, Germany.
3 Developmental Biology, Max Delbrück Center for Molecular Medicine, Berlin, Germany.
4 DZHK (German Center for Cardiovascular Research), Partner Site Greifswald, Germany.
5 Berlin Institute of Health (BIH), Berlin, Germany.

Muscle atrophy was investigated by morphological and histological analyses. After 96 hours, loss of *gp130* attenuated CLP induced muscular atrophy as indicated by a reduced loss of muscle weight (Fig. 1*A*) and MCSA (Fig. 1*B*) of *tibialis anterior* and *gastrocnemius/plantaris* muscles. As expected, quantitative RT-PCR showed a decreased gp130 mediated signaling, as indicated by *Socs3* expression, in CLP cKO compared to controls. After 96 hours of CLP, controls showed an increased *Trim63*, *Fbxo32* and *Sqstm1* mRNA expression which were unaltered in CLP cKO.

Cell culture analysis of differentiated C2C12 myocytes showed that IL-6 induces the JAK/STAT pathway and causes myotube atrophy via gp130 as indicated by a reduction of myotube diameters after 24 and 72 hours of IL-6 treatment.

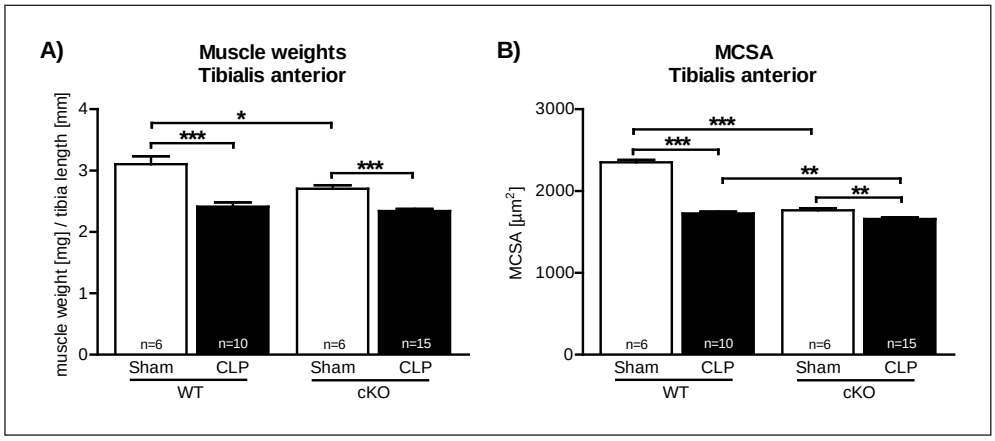

Fig. 1 Deletion of gp130 in myocytes attenuates inflammation-induced muscle atrophy: Gp130 WT and cKO mice were subjected to CLP and sham surgery, respectively. 96 hours after surgery muscle weights normalized to tibia length (*A*) and MCSAs of fast/type II myofibers (*B*) were measured in tibialis anterior muscle. Loss of gp130 leads to a reduction of muscle weight and MCSA and attenuates loss of muscle weight and fast/type II fiber MCSA during sepsis. All values are mean ± SEM; *p<0.05; **p<0.01; ***p<0.001.

Conclusion: The IL-6 receptor gp130 plays a key role in inflammation-induced skeletal muscle atrophy possibly involving the JAK/STAT signaling pathway.

References

Bierbrauer, J., Koch, S., Olbricht, C., Hamati, J., Lodka, D., Schneider, J., Luther-Schröder, A., Kleber, C., Faust, K., Wiesener, S., Spies, C. D., Spranger, J., Spuler, S., Fielitz, J., and Weber-Carstens, S.: Early type II fiber atrophy in intensive care unit patients with nonexcitable muscle membrane. Crit. Care Med. *40*/2, 647–650 (2012)

Hermans, G., Van Mechelen, H., Clerckx, B., Vanhullebusch, T., Mesotten, D., Wilmer, A., Casaer, M. P., Meersseman, P., Debaveye, Y., Van Cromphaut, S., Wouters, P., Gosselink, R., and Van den Berghe, G.:: Acute outcomes and 1-year mortality of intensive care unit-acquired weakness. A cohort study and propensity-matched analysis. Amer. J. Respir. Crit. Care Med. *190*/4, 410–420 (2014)

Langhans, C., Weber-Carstens, S., Schmidt, F., Hamati, J., Kny, M., Zhu, X., Wollersheim, T., Koch, S., Krebs, M., Schulz, H., Lodka, D., Saar, K., Labeit, S., Spies, C., Hubner, N., Spranger, J., Spuler, S., Boschmann, M., Dittmar, G., Butler-Browne, G., Mouly, V., and Fielitz, J.: Inflammation-induced acute phase response in skeletal muscle and critical illness myopathy. PLoS One *9*/3, e92048 (2014)

Wollersheim, T., Woehlecke, J., Krebs, M., Hamati, J., Lodka, D., Luther-Schroeder, A., Langhans, C., Haas, K., Radtke, T., Kleber, C., Spies, C., Labeit, S., Schuelke, M., Spuler, S., Spranger, J., Weber-Carstens, S., and Fielitz, J.: Dynamics of myosin degradation in intensive care unit-acquired weakness during severe critical illness. Intensive Care Med. *40*/4, 528–538. doi: 10.1007/s00134-014-3224-9 (2014)

Zhu, X., Kny, M., Schmidt, F., Hahn, A., Wollersheim, T., Kleber, C., Weber-Carstens, S., and Fielitz, J.: Secreted frizzled-related protein 2 and inflammation-induced skeletal muscle atrophy. Crit. Care Med. *45*/2, e169–e183. doi: 10.1097/CCM.0000000000002056 (2017)

Prof. Dr. Jens Fielitz
Dr. Melanie Kny
Lukas Zanders
Department of Molecular Cardiology
Experimental and Clinical Research Center (ECRC)
Charité – Universitätsmedizin Berlin
Charité Campus Buch
Lindenberger Weg 80
13125 Berlin
Germany
Tel.: +49 30 450540424/421
Fax: +49 30 450540928
E-Mail: jens.fielitz@charite.de
Melanie.Kny@charite.de
lukas.zanders@charite.de

Prof. Dr. Matthias Selbach
Dr. Erik McShane
Proteome Dynamics
Max Delbrück Center for Molecular Medicine
Robert-Rössle-Straße 10
13092 Berlin
Germany
Tel.: +49 30 94063574
Fax: +49 30 94062394
E-Mail: matthias.selbach@mdc-berlin.de

Dr. Ines Lahmann
Prof. Dr. Carmen Birchmeier
Developmental Biology
Max-Delbrück-Center for Molecular Medicine
Robert-Rössle-Straße 10
13092 Berlin
Germany
Tel.: +49 30 94062864
+49 30 94063313
E-Mail: ines.lahmann@mdc-berlin.de
cbirch@mdc-berlin.de

ISSN: 0369-5034
ISBN: 978-3-8047-3849-2