Appendix

Effects of Intraoperative High PEEP with Recruitment Maneuvers vs. Low PEEP on Postoperative Pulmonary Complications – A patient–level meta–analysis of three randomized clinical trials

LIST OF COLLABORATORS

THE PROVHILO INVESTIGATORS

Steering and executive committees

Sabrine NT Hemmes,[1] Marcelo Gama de Abreu,[2] Paolo Severgnini,[3] Markus W Hollmann,[1] Jan M Binnekade,[4] Hermann Wrigge,[5] Jaume Canet,[6] Michael Hiesmayr,[7] Werner Schmid,[7] Edda Tschernko,[7] Samir Jaber,[8] Göran Hedenstierna,[9] Christian Putensen,[10] Paolo Pelosi,[11,12] Marcus J Schultz[4,13,14]

Amsterdam UMC, University of Amsterdam, Amsterdam, The Netherlands
[1]Department of Anaesthesiology
[4]Department of Intensive Care
[14]Department of Intensive Care & Laboratory of Experimental Intensive Care and Anesthesiology (L·E·I·C·A)

University Hospital Carl Gustav Carus, Technische Universität Dresden, Dresden, Germany
[2]Pulmonary Engineering Group, Department of Anesthesiology and Intensive Care Medicine

University of Insubria, Varese, Italy
[3]Department of Biotechnologies and Sciences of Life

University of Leipzig, Leipzig, Germany
[5]Department of Anesthesiology and Intensive Care Medicine

Hospital Universitari Germans Trias I Pujol, Barcelona, Spain
[6]Department of Anesthesiology

Medical University Vienna, Vienna, Austria
[7]Division of Cardiac, Thoracic, and Vascular Anesthesia and Intensive Care

Saint Eloi University Hospital, Montpellier, France
[8]Department of Critical Care Medicine and Anesthesiology (SAR B)

Uppsala University, Uppsala, Sweden
[9]Department of Medical Sciences, Clinical Physiology

University Hospital Bonn, Bonn, Germany
[10]Dept. of Anesthesiology and Intensive Care Medicine

[11]IRCCS San Martino Policlinico Hospital, Genoa, Italy

University of Genoa, Genoa, Italy
[12]Department of Surgical Sciences and Integrated Diagnostics (DISC)

Mahidol University, Bangkok, Thailand
[13]Mahidol Oxford Tropical Medicine Research Unit (MORU), Faculty of Tropical Medicine

Investigators

(*, *indicates local principal investigators; names are listed in alphabetical order*)

Agnes Marti	Hospital Universitari Germans Trias I Pujol, Spain
Alessandro Bacuzzi	University of Insubria - Azienda Ospedaliera Fondazione Macchi - Ospedale di Circolo, Italy
Alexander Brodhun	Johannes Gutenberg - Universität Mainz, Germany
Alexandre Molin*	Università degli Studi di Genova, IRCCS San Martino IST, Italy
Alfred Merten	Hospital Sant Pau, Spain
Ana Parera	Hospital Sant Pau, Spain
Andrea Brunelli*	Hospital Universitari Germans Trias I Pujol, Spain
Andrea Cortegiani	Università degli Studi di Palermo, Italy

Andreas Güldner	University Hospital Dresden, Technische Universität Dresden, Germany
Andreas W Reske	University of Leipzig, Germany
Angelo Gratarola	Università degli Studi di Genova, IRCCS San Martino IST, Italy
Antonino Giarratano*	Università degli Studi di Palermo, Italy
Bea Bastin	Düsseldorf University Hospital, Heinrich-Heine University Düsseldorf, Germany
Bjorn Heyse	Ghent University Hospital, Belgium
Branka Mazul-Sunko*	University Hospital Sveti Duh, Croatia
Bruno Amantea	University "Magna Graecia" of Catanzaro, Italy
Bruno Barberis	Azienda Sanitaria Locale TO3 - Ospedale di Rivoli, Italy
Christian Putensen*	University Hospital of Bonn Medical School, Germany
Christopher Uhlig	University Hospital Dresden, Technische Universität Dresden, Germany
Conrado Minguez Marín	Consorcio Hospital General Universitario Valencia, Spain
Cristian Celentano	Azienda Sanitaria Locale TO3 - Ospedale di Rivoli, Italy
Daniela La Bella	University of Foggia, Italy
David D'Antini	University of Foggia, Italy
David Velghe*	ZNA Middelheim, Belgium
Demet Sulemanji	Massachusetts General Hospital, USA
Edoardo De Robertis*	University of Napoli Federico II, Italy
Eric Hartmann	Johannes Gutenberg - Universität Mainz, Germany
Francesca Montalto	Università degli Studi di Palermo, Italy
Francesco Tropea	University "Magna Graecia" of Catanzaro, Italy
Gary H Mills*	Sheffield Teaching Hospitals, United Kingdom
Gilda Cinnella*	University of Foggia, Italy
Giorgio Della Rocca*	Università degli Studi di Udine, Italy
Girolamo Caggianelli	University of Foggia, Italy
Giulia Pellerano	Università degli Studi di Genova, IRCCS San Martino IST, Italy
Giuseppina Mollica	University of Foggia, Italy
Guillermo Bugedo*	Hospital Clínico de la Pontificia Universidad Católica de Chile, Chile
Hermann Wrigge*	University of Leipzig, Germany
Jan-Paul Mulier*	AZ St Jan, Belgium
Jeroen Vandenbrande	Virga Jesse Ziekenhuis, Belgium
Johann Geib	Düsseldorf University Hospital, Heinrich-Heine University Düsseldorf, Germany
Jonathan Yaqub	University Hospital Dresden, Technische Universität Dresden, Germany
Jorge Florez	Hospital Clínico de la Pontificia Universidad Católica de Chile, Chile
Juan F Mayoral	Fundación Puigvert, Spain
Juraj Sprung*	Mayo Clinic, USA
Jurgen Van Limmen	Ghent University Hospital, Belgium
Lieuwe DJ Bos	Academic Medical Center, University of Amsterdam, The Netherlands
Luc de Baerdemaeker	Ghent University Hospital, Belgium
Luc Jamaer*	Virga Jesse Ziekenhuis, Belgium
Luigi Spagnolo*	Azienda Sanitaria Locale TO3 - Ospedale di Rivoli, Italy
Lydia Strys	Johannes Gutenberg - Universität Mainz, Germany
Manuel Granell Gil*	Consorcio Hospital General Universitario Valencia, Spain
Marcelo Gama de Abreu*	University Hospital Dresden, Technische Universität Dresden, Germany
Marcos F Vidal Melo*	Massachusetts General Hospital, USA
Marcus J Schultz*	Academic Medical Center, University of Amsterdam, The Netherlands
Maria Carmen Unzueta*	Hospital Sant Pau, Spain
Maria Victoria Moral	Hospital Sant Pau, Spain

Marion Ferner	Johannes Gutenberg - Universität Mainz, Germany
Markus W Hollmann	Academic Medical Center, University of Amsterdam, The Netherlands
Martin Weiss	Düsseldorf University Hospital, Heinrich-Heine University Düsseldorf, Germany
Massimo Vanoni	University of Insubria - Azienda Ospedaliera Fondazione Macchi - Ospedale di Circolo, Italy
Maximilian S Schaefer	Düsseldorf University Hospital, Heinrich-Heine University Düsseldorf, Germany
Mercè Prieto	Fundación Puigvert, Spain
Michele Grio	Azienda Sanitaria Locale TO3 - Ospedale di Rivoli, Italy
Paolo Severgnini*	University of Insubria - Azienda Ospedaliera Fondazione Macchi - Ospedale di Circolo, Italy
Peter Markus Spieth	University Hospital Dresden, Technische Universität Dresden, Germany
Philipp Simon	University of Leipzig, Germany
Phoebe Bodger*	Barts Health NHS Trust, United Kingdom
Pilar Sierra	Fundación Puigvert, Spain
Rita Laufenberg-Feldmann*	Johannes Gutenberg - Universität Mainz, Germany
Roberta Rusca	Università degli Studi di Genova, IRCCS San Martino IST, Italy
Rodolfo Proietti*	Università degli Studi di Roma Cattolica, Italy
Sabrine NT Hemmes	Academic Medical Center, University of Amsterdam, The Netherlands
Santi Maurizio Raineri	Università degli Studi di Palermo, Italy
Santo Caroleo*	University "Magna Graecia" of Catanzaro, Italy
Sergi Sabaté*	Fundación Puigvert, Spain
Stefan De Hert*	Ghent University Hospital, Belgium
Stefano Pezzato	Università degli Studi di Genova, IRCCS San Martino IST, Italy
Tanja A Treschan*	Düsseldorf University Hospital, Heinrich-Heine University Düsseldorf, Germany
Tatjana Goranovic	University Hospital Sveti Duh, Croatia
Thea Koch	University Hospital Dresden, Technische Universität Dresden, Germany
Thomas Bluth	University Hospital Dresden, Technische Universität Dresden, Germany
Thomas Kiss	University Hospital Dresden, Technische Universität Dresden, Germany
Valter Perilli	Università degli Studi di Roma Cattolica, Italy
Virginia Cegarra	Hospital Sant Pau, Spain
Werner Schmid*	Medical University Viena, Viena

Information and funding
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THE iPROVE INVESTIGATORS

Steering and executive committees

Carlos Ferrando,[1,2] Javier Belda,[3] Marina Soro,[4] Jaume Canet,[5] Carmen Unzueta,[6] Fernando Suarez-Sipmann,[7] Julián Librero,[8] Alicia Llombart,[9] Lucas Rovira,[10] Manuel Granell,[10] César Aldecoa,[11] Oscar Diaz-Cambronero,[12] Jaume Balust,[13] Ignacio Garutti,[14] Rafael Gonzalez,[15] Lucia Gallego,[16] Santiago Garcia del Valle,[17] Javier Redondo,[18] David Pestaña,[19] Aurelio Rodríguez,[20] Javier García,[21] Manuel de la Matta,[22] Maite Ibáñez,[23] Francisco Barrios,[24] Samuel Hernández,[25] Vicente Torres,[26] Salvador Peiró,[27] Natividad Pozo[28]

Hospital Clinic de Barcelona, Barcelona, Spain
[1]Department of Anesthesiology and Critical Care

[2]CIBER of Respiratory Disease, Instituto de Salud Carlos III, Madrid, Spain

Medicine Faculty, Universidad de Valencia, Valencia, Spain
[3]Department of Surgery

Hospital Clínico Universitario de Valencia, Valencia, Spain
[4]Department of Anesthesiology and Critical Care

Hospital Universitario Germans Tries i Pujol, Barcelona, Spain
[5]Department of Anesthesiology and Critical Care

Hospital Universitario San Pau, Barcelona, Spain
[6]Department of Anesthesiology and Critical Care

Hospital Universitario La Princesa, Madrid, Spain
[7]Department of Anesthesiology and Critical Care

Red de Investigación en Servicios de Salud en Enfermedades Crónicas (REDISSEC), Pamplona, Spain
[8]Navarrabiomed-Fundación Miguel Servet

Corachan Hospital, Barcelona, Spain
[9]Department of Pharmacology

Hospital General Universitario de Valencia, Valencia, Spain
[10]Department of Anesthesiology and Critical Care

Hospital Universitario Río Hortega, Valladolid, Spain
[11]Department of Anesthesiology and Critical Care

Hospital Universitario y Politécnico La Fe, Valencia, Spain
[12]Department of Anesthesiology and Critical Care
[27]IISLAFE Clinical Research Institute

Hospital Clínic i Provincial Universitario de Barcelona, Barcelona, Spain
[13]Department of Anesthesiology and Critical Care

Hospital General Universitario Gregorio Marañón, Madrid, Spain
[14]Department of Anesthesiology and Critical Care

Hospital de León, León, Spain
[15]Department of Anesthesiology and Critical Care

Hospital Universitario Miguel Servet de Zaragoza, Zaragoza, Spain
[16]Department of Anesthesiology and Critical Care

Hospital Fundación de Alcorcón, Alcorcón, Spain
[17]Department of Anesthesiology and Critical Care

Hospital General Universitario de Ciudad Real, Ciudad Real, Spain
[18]Department of Anesthesiology and Critical Care

Hospital Universitario Ramón y Cajal, Madrid, Spain
[19]Department of Anesthesiology and Critical Care

Hospital de Gran Canaria, Dr. Negrín, Gran Canaria, Spain
[20]Department of Anesthesiology and Critical Care

Hospital Universitario Puerta de Hierro de Majadahonda, Madrid, Spain
[21]Department of Anesthesiology and Critical Care

Hospital Universitario Virgen del Rocio de Sevilla, Sevilla, Spain
[22]Department of Anesthesiology and Critical Care

Hospital de la Marina Baixa de la Vila Joiosa, Alicante, Spain
[23]Department of Anesthesiology

Hospital Principe de Asturias, Madrid, Spain
[24]Department of Anesthesiology and Critical Care

Hospital NS de Candelaria, Santa Cruz de Tenerife, Spain
[25]Department of Anesthesiology

Hospital Son Espases de Mallorca, Mallorca, Spain
[26]Department of Anesthesiology and Critical Care

[28]INCLIVA, Biomedical Research Institute, Valencia, Spain

Investigators

(*names are listed in alphabetical order*)

Abigail Villena	Hospital Clínico Universitario de Valencia, Valencia, Spain
Albert Carramiñana	Hospital Universitario Germans Tries i Pujol, Badalona, Spain
Alberto Gallego-Casilda	Hospital Universitario Miguel Servet de Zaragoza, Zaragoza, Spain
Alejandro Duca	Hospital Clínico Universitario de Valencia, Valencia, Spain
Amalia Alcón	Hospital Clínic i Provincial Universitario de Barcelona, Barcelona, Spain
Amanda Miñana	Hospital Clínico Universitario de Valencia, Valencia, Spain
Ana Asensio	Hospital Universitario Miguel Servet de Zaragoza, Zaragoza, Spain
Ana Colás	Hospital Universitario Miguel Servet de Zaragoza, Zaragoza, Spain
Ana Isabel Galve	Hospital General Universitario Gregorio Marañón, Madrid, Spain
Ana Izquierdo	Hospital Clínico Universitario de Valencia, Valencia, Spain
Ana Jurado	Hospital Clínico Universitario de Valencia, Valencia, Spain
Ana María Pérez	Hospital de León, León, Spain
Ana Mugarra	Hospital Clínico Universitario de Valencia, Valencia, Spain
Ana Parera	Hospital Universitario San Pau, Barcelona, Spain
Andrea Brunelli	Hospital Universitario Germans Tries i Pujol, Badalona, Spain
Andrea Gutierrez	Hospital Clínico Universitario de Valencia, Valencia, Spain
Ángeles De Miguel	Hospital General Universitario Gregorio Marañón, Madrid, Spain
Angels Lozano	Hospital Clínico Universitario de Valencia, Valencia, Spain
Antonio Katime	Hospital Clínico Universitario de Valencia, Valencia, Spain
Antonio Romero	Hospital Universitario Puerta de Hierro de Majadahonda, Madrid, Spain

Beatriz Garrigues	Hospital Clínico Universitario de Valencia, Valencia, Spain
Begoña Ayas	Hospital Universitario y Politécnico La Fe, Valencia, Spain
Blanca Arocas	Hospital Clínico Universitario de Valencia, Valencia, Spain
Carlos Delgado	Hospital Clínico Universitario de Valencia, Valencia, Spain
Carmen Fernández	Hospital General Universitario Gregorio Marañón, Madrid, Spain
Carolina Romero	Hospital Clínico Universitario de Valencia, Valencia, Spain
Clara Gallego	Hospital Universitario Ramón y Cajal, Madrid, Spain
Cristina Garcés	Hospital Universitario Miguel Servet de Zaragoza, Zaragoza, Spain
Cristina Lisbona	Hospital General Universitario Gregorio Marañón, Madrid, Spain
Cristina Parrilla	Hospital Clínico Universitario de Valencia, Valencia, Spain
Daniel López-Herrera	Hospital Universitario Virgen del Rocio de Sevilla, Sevilla, Spain
Domingo González	Hospital Universitario Virgen del Rocio de Sevilla, Sevilla, Spain
Eduardo Llamazares	Hospital General Universitario Gregorio Marañón, Madrid, Spain
Elena Del Rio	Hospital Clínico Universitario de Valencia, Valencia, Spain
Elena Lozano	Hospital de la Marina Baixa de la Vila Joiosa, Alicante, Spain
Ernesto Pastor	Hospital Clínico Universitario de Valencia, Valencia, Spain
Estefanía Chamorro	Hospital General Universitario Gregorio Marañón, Madrid, Spain
Estefanía Gracia	Hospital Clínico Universitario de Valencia, Valencia, Spain
Ester Sánchez	Hospital de la Marina Baixa de la Vila Joiosa, Alicante, Spain
Esther Romero	Hospital Clínico Universitario de Valencia, Valencia, Spain
Fernando Díez	Hospital de León, León, Spain
Ferran Serralta	Hospital Clínico Universitario de Valencia, Valencia, Spain
Francisco Daviu	Hospital General Universitario Gregorio Marañón, Madrid, Spain
Francisco Sandín	Hospital Universitario Miguel Servet de Zaragoza, Zaragoza, Spain
Gerardo Aguilar	Hospital Clínico Universitario de Valencia, Valencia, Spain
Gerardo Tusman	Hospital Privado de Comunidad, Mar del Plata, Buenos Aires, Argentina
Gonzalo Azparren	Hospital Universitario San Pau, Barcelona, Spain
Graciela Martínez-Pallí	Hospital Clínic i Provincial Universitario de Barcelona, Barcelona, Spain
Guido Mazzinari	Hospital de Manises, Valencia, Spain
Inmaculada Benítez	Hospital Universitario Virgen del Rocio de Sevilla, Sevilla, Spain
Inmaculada Hernandéz	Hospital General Universitario Gregorio Marañón, Madrid, Spain
Inmaculada India	Hospital Universitario San Pau, Barcelona, Spain
Irene León	Hospital Clínic i Provincial Universitario de Barcelona, Barcelona, Spain
Isabel Fuentes	Hospital Clínico Universitario de Valencia, Valencia, Spain
Isabel Ruiz	Hospital Universitario Ramón y Cajal, Madrid, Spain
Jaume Puig	Hospital Clínico Universitario de Valencia, Valencia, Spain
Javie Ignacio Román	Hospital Son Espases de Mallorca, Mallorca, Spain
Jesús Acosta	Hospital Universitario Virgen del Rocio de Sevilla, Sevilla, Spain
Jesús Rico-Feijoo	Hospital Universitario Río Hortega, Valladolid, Spain
Jonathan Olmedo	Hospital General Universitario Gregorio Marañón, Madrid, Spain
Jose A. Carbonell	Hospital Clínico Universitario de Valencia, Valencia, Spain
Jose M. Alonso	Hospital Clínico Universitario de Valencia, Valencia, Spain
Jose María Pérez	Hospital General Universitario Gregorio Marañón, Madrid, Spain

Jose Miguel Marcos	Hospital de León, León, Spain
Jose Navarro	Hospital Clínico Universitario de Valencia, Valencia, Spain
Jose Valdivia	Hospital de la Marina Baixa de la Vila Joiosa, Alicante, Spain
Juan Carrizo	Hospital Clínico Universitario de Valencia, Valencia, Spain
Laura Piqueras	Hospital Clínico Universitario de Valencia, Valencia, Spain
Laura Soriano	Hospital General Universitario Gregorio Marañón, Madrid, Spain
Laura Vaquero	Hospital Universitario Río Hortega, Valladolid, Spain
Lisset Miguel	Hospital Universitario Ramón y Cajal, Madrid, Spain
Lorena Muñoz	Hospital General Universitario de Valencia, Valencia, Spain
Lucia Valencia	Hospital de Gran Canaria, Dr. Negrín, Gran Canaria, Spain
Luis Olmedilla	Hospital General Universitario Gregorio Marañón, Madrid, Spain
Mª Justina Etulain	Hospital General Universitario Gregorio Marañón, Madrid, Spain
Manuel Tisner	Hospital General Universitario Gregorio Marañón, Madrid, Spain
María Barrio	Hospital General Universitario Gregorio Marañón, Madrid, Spain
María Dolores Alonso	Hospital General Universitario de Valencia, Valencia, Spain
María García	Hospital Universitario Río Hortega, Valladolid, Spain
María J. Hernández	Hospital General Universitario de Valencia, Valencia, Spain
María José Alberola	Hospital Universitario y Politécnico La Fe, Valencia, Spain
María Parra	Hospital Clínico Universitario de Valencia, Valencia, Spain
María Pilar Argente	Hospital Universitario y Politécnico La Fe, Valencia, Spain
María Vila	Hospital Universitario y Politécnico La Fe, Valencia, Spain
Mario De Fez	Hospital Clínico Universitario de Valencia, Valencia, Spain
Marta Agilaga	Hospital Universitario San Pau, Barcelona, Spain
Marta Gine	Hospital Universitario San Pau, Barcelona, Spain
Mercedes Ayuso	Hospital Principe de Asturias, Madrid, Spain
Mercedes García	Hospital Universitario San Pau, Barcelona, Spain
Natalia Bejarano	Hospital General Universitario de Ciudad Real, Ciudad Real, Spain
Natalia Peña	Hospital Universitario Miguel Servet de Zaragoza, Zaragoza, Spain
Nazario Ojeda	Hospital de Gran Canaria, Dr. Negrín, Gran Canaria, Spain
Nilda Martínez	Hospital Universitario Ramón y Cajal, Madrid, Spain
Nuria García	Hospital Universitario y Politécnico La Fe, Valencia, Spain
Oto Padrón	Hospital de Gran Canaria, Dr. Negrín, Gran Canaria, Spain
Pablo García	Hospital Fundación de Alcorcón, Alcorcón, Spain
Paola Valls	Hospital Clínico Universitario de Valencia, Valencia, Spain
Patricia Cruz	Hospital General Universitario Gregorio Marañón, Madrid, Spain
Patricia Piñeiro	Hospital General Universitario Gregorio Marañón, Madrid, Spain
Pedro Charco	Hospital Clínico Universitario de Valencia, Valencia, Spain
Rafael Anaya	Hospital Universitario San Pau, Barcelona, Spain
Ramiro López	Hospital General Universitario Gregorio Marañón, Madrid, Spain
Rayco Rodríguez	Hospital de Gran Canaria, Dr. Negrín, Gran Canaria, Spain
Rocío Martínez	Hospital General Universitario Gregorio Marañón, Madrid, Spain
Roger Pujol	Hospital Clínic i Provincial Universitario de Barcelona, Barcelona, Spain
Rosa Dosdá	Hospital Clínico Universitario de Valencia, Valencia, Spain
Rosa Lardies	Hospital Clínic i Provincial Universitario de Barcelona, Barcelona, Spain
Ruben Díaz	Hospital Universitario San Pau, Barcelona, Spain
Rubén Villazala	Hospital General Universitario de Ciudad Real, Ciudad Real, Spain

Sara Zapatero	Hospital General Universitario Gregorio Marañón, Madrid, Spain
Sergio Cabrera	Hospital de Gran Canaria, Dr. Negrín, Gran Canaria, Spain
Sergio Sánchez	Hospital General Universitario de Ciudad Real, Ciudad Real, Spain
Silvia Martin	Hospital Universitario Río Hortega, Valladolid, Spain
Suzana Diaz	Hospital General Universitario Gregorio Marañón, Madrid, Spain
Tania Franco	Hospital Universitario Ramón y Cajal, Madrid, Spain
Tania Moreno	Hospital Clínico Universitario de Valencia, Valencia, Spain
Tania Socorro	Hospital Clínico Universitario de Valencia, Valencia, Spain
Vicente Gilabert	Hospital de la Marina Baixa de la Vila Joiosa, Alicante, Spain
Victor Balandrón	Hospital General Universitario de Ciudad Real, Ciudad Real, Spain
Victoria Moral	Hospital Universitario San Pau, Barcelona, Spain
Virgina Cegarra	Hospital Universitario San Pau, Barcelona, Spain
Viviana Varón	Hospital Fundación de Alcorcón, Alcorcón, Spain

Information and funding

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THE PROBESE INVESTIGATORS

Writing, steering and executive committees

Thomas Bluth,[1] Ary Serpa Neto,[2,3,4] Ilona Bobek,[5] Jaume Canet,[6] Gilda Cinnella,[7] Luc de Baerdemaeker,[8] Cesare Gregoretti,[9] Göran Hedenstierna,[10] Sabrine NT Hemmes,[11] Michael Hiesmayr,[12] Markus W Hollmann,[11] Samir Jaber,[13] John Laffey,[14] Marc-Joseph Licker,[15] Klaus Markstaller,[16] Idit Matot,[17] Gary H Mills,[18] Jan Paul Mulier,[19] Christian Putensen,[20] Rolf Rossaint,[21] Jochen Schmitt,[22] Mert Senturk,[23] Paolo Severgnini,[24] Juraj Sprung,[25] Marcos F Vidal Melo,[26] Hermann Wrigge,[27,28] Marcus J Schultz,[3,29] Paolo Pelosi,[30,31] Marcelo Gama de Abreu[1]

University Hospital Carl Gustav Carus, Technische Universität Dresden, Dresden, Germany
[1]Pulmonary Engineering Group, Department of Anesthesiology and Intensive Care Medicine
[22]Center for Evidence-based Healthcare

Hospital Israelita Albert Einstein, São Paulo, Brazil
[2]Department of Critical Care Medicine

Amsterdam UMC, University of Amsterdam, Amsterdam, The Netherlands [3]Department of Intensive Care & Laboratory of Experimental Intensive Care and Anesthesiology (L·E·I·C·A)
[11]Department of Anaesthesiology

Instituto do Coração, Hospital das Clinicas HCFMUSP, Faculdade de Medicina, Universidade de Sao Paulo, Sao Paulo, Brazil
[4]Cardio-Pulmonary Department, Pulmonary Division

Semmelweis Egyetem, Budapest, Hungary
[5]Aneszteziológiai és Intenzív Terápiás Klinika

Hospital Universitari Germans Trias I Pujol, Barcelona, Spain
[6]Department of Anesthesiology

Unviersity of Foggia, Foggia, Italy
[7]Department of Anesthesiology and Intensive Care Medicine

Ghent University Hospital, Ghent, Belgium
[8]Department of Anesthesiology and Perioperative Medicine

Città della Salute e dela Scienza, Turin, Italy
[9]Department of Anesthesiology

Uppsala University, Uppsala, Sweden
[10]Department of Medical Sciences, Clinical Physiology

Medical University Vienna, Vienna, Austria
[12]Division of Cardiac, Thoracic, and Vascular Anesthesia and Intensive Care
[16]Department of Anaesthesia, Critical Care and Pain Medicine

Saint Eloi University Hospital, Montpellier, France
[13]Department of Critical Care Medicine and Anesthesiology (SAR B)

St. Michael's Hospital, University of Toronto, Toronto, Canada
[14]Department of Anesthesiology

University Hospitals of Geneva, Geneva, Switzerland
[15]Division of Anesthesiology

Tel-Aviv Medical Center, Sackler Medical School, Tel Aviv, Israel
[17]Departmen of Anesthesia, Pain and Critical Care

Sheffield Teaching Hospitals, University of Sheffield, Sheffield, United Kingdom

[18]Operating Services, Critical Care and Anaesthesia (OSCCA)

AZ Sint Jan Brugge-Oostende AV, Brugge, Belgium
[19]Department of Anesthesiology

University Hospital Bonn, Bonn, Germany
[20]Department of Anesthesiology and Intensive Care Medicine

Medical Faculty, RWTH Aachen University, Aachen, Germany
[21]Department of Anesthesiology

Istanbul University, Istanbul Faculty of Medicine, Istanbul, Turkey
[23]Department of Anesthesiology and Intensive Care

Universita' dell'Insubria, Azienda Ospedaliera ASST Sette Laghi Ospedale di Circolo e Fondazione Macchi, Varese, Italy
[24]Dipartimento di Anestesia

Mayo Clinic, Rochester, Minnesota, USA
[25]Department of Anesthesiology and Perioperative Medicine

Massachusetts General Hospital, Boston, Massachusetts, USA
[26]Department of Anesthesia, Critical Care and Pain Medicine
University of Leipzig, Leipzig, Germany
[27]Department of Anesthesiology and Intensive Care Medicine

Bergmannstrost Hospital Halle, Halle, Germany
[28]Department of Anaesthesiology, Intensive Care and Emergency Medicine, Pain Therapy

Mahidol University, Bangkok, Thailand
[29]Mahidol Oxford Tropical Medicine Research Unit (MORU), Faculty of Tropical Medicine

[30]IRCCS San Martino Policlinico Hospital, Genoa, Italy

University of Genoa, Genoa, Italy
[31]Department of Surgical Sciences and Integrated Diagnostics (DISC)

Investigators

(**, indicates local principal investigators; names are listed in alphabetical order*)

Abelha, Fernando*	Centro Hospitalar de São João, Department of Anaesthesiology, Porto, Portugal and Department of Surgery and Physiology, Cardiovascular Research Center, Faculty of Medicine of the University of Porto, Porto, Portugal
Abitağaoğlu, Sühayla	Fatih Sultan Mehmet Educational and Research Hospital, İstanbul, Turkey
Achilles, Marc*	Marienhospital Wesel, Wesel, Germany
Adebesin, Afeez	Imperial College Healthcare NHS Trust, UK
Adriaensens, Ine	University Hospital Antwerp, Belgium
Ahene, Charles*	Cleveland Clinic Abu Dhabi, Al Maryah Island, Abu Dhabi, UAE
Akbar, Fatima	Imperial College Healthcare NHS Trust, UK
Al Harbi, Mohammed	Ministry of National Guard Health Affairs, King Abdulaziz Medical City – Riyadh, Anesthesia Department and King Saud Bin Abdulaziz University for Health science, Saudi Arabia
Al Khoury al Kallab, Rita	Hôpitaux Universitaires de Genève, Département APSI, service d'anesthésiologie, Switzerland

Albanel, Xavier	Hôpitaux Universitaires de Genève, Département APSI, service d'anesthésiologie, Switzerland
Aldenkortt, Florence	Hôpitaux Universitaires de Genève, Département APSI, service d'anesthésiologie, Switzerland
Alfouzan, Rawan Abdullah Saleh	Ministry of National Guard Health Affairs, King Abdulaziz Medical City – Riyadh, Anesthesia Department, Saudi Arabia
Alruqaie, Reef	Ministry of National Guard Health Affairs, King Abdulaziz Medical City – Riyadh, Anesthesia Department, Saudi Arabia
Altermatt, Fernando*	Department of Anesthesiology. School of Medicine. Pontificia Universidad Catolica de Chile
Araujo, Bruno Luís de Castro*	Department of Anesthesiology, Hospital do Câncer II, National Cancer Institute of Brazil (INCA), Rio de Janeiro, Brazil
Arbesú, Genaro	University Hospital Germans Trias i Pujol, ICS, UAB, Spain
Artsi, Hanna	Division of Anesthesia, Pain and Critical Care, Tel-Aviv Medical Center affiliated with Sackler Medical School, Tel Aviv University, Tel Aviv, Israel
Aurilio, Caterina*	Department of Women, child and General and Specialized Surgery. University of Campania "L. Vanvitelli", Italy.
Ayanoglu, Omer Hilmi	Marmara University Pendik Training and Research Hospital, Turkey
Bacuzzi, Alessandro	Universita' dell'Insubria – Dipartimento di Anestesia - Azienda Ospedaliera Asst Settlaghi Ospedale di Circolo e Fondazione Macchi – 21100 Varese - Italy
Baig, Harris*	University of Mississippi Medical Center, MS, USA
Baird, Yolanda	St Richard's Hospital, Chichester, UK
Balonov, Konstantin*	Department of Anesthesiology and Perioperative Medicine, Tufts Medical Center, Boston, MA, USA
Balust, Jaume	Department of Anaesthesiology, Hospital Clínic, Barcelona, Spain.
Banks, Samantha	Royal Cornwall Hospital NHS Trust, UK
Bao, Xiaodong	Department of Anesthesia, Critical Care and Pain Medicine, Massachusetts General Hospital, Boston, Massachusetts, USA
Baumgartner, Mélanie	Hôpitaux Universitaires de Genève, Département APSI, service d'anesthésiologie, Switzerland
Belda Tortosa, Isabel*	Hospital Sagrat Cor- Barcelona, Spain
Bergamaschi, Alice	Department of Anesthesiology and Intensive Care, Pulmonary Engineering Group, University Hospital Carl Gustav Carus, Technische Universität Dresden, Germany
Bergmann, Lars*	Klinik für Anästhesiologie, Intensivmedizin und Schmerztherapie, Universitätsklinikum Knappschaftskrankenhaus Bochum, Bochum, Germany
Bigatello, Luca*	St. Elizabeth's Medical Center, MA, USA
Biosca Pérez, Elena	Consorcio Hospital General Universitario of Valencia, Spain
Birr, Katja	Department of Anesthesiology and Intensive Care, Pulmonary Engineering Group, University Hospital Carl Gustav Carus, Technische Universität Dresden, Germany
Bluth, Thomas	Department of Anesthesiology and Intensive Care, Pulmonary Engineering Group, University Hospital Carl Gustav Carus, Technische Universität Dresden, Germany
Bojaxhi, Elird	Department of Anesthesiology and Perioperative Medicine, Mayo Clinic Jacksonville, USA
Bonenti, Chiara	Universita' dell'Insubria – Dipartimento di Anestesia - Azienda Ospedaliera Asst Settlaghi Ospedale di Circolo e Fondazione Macchi – 21100 Varese - Italy
Bonney, Iwona	Department of Anesthesiology and Perioperative Medicine, Tufts Medical Center, Boston, MA, USA
Bos, Elke M.E.	Amsterdam UMC, University of Amsterdam, Department of Anesthesiology, Meibergdreef 9, Amsterdam, The Netherlands
Bowman, Sara	Homerton University Hospitals NHS Foundation Trust, UK

Braz, Leandro Gobbo	Department of Anesthesiology, Universidade Estadual Paulista, Botucatu/SP, Brazil
Brugnoni, Elisa	Universita' dell'Insubria – Dipartimento di Anestesia - Azienda Ospedaliera Asst Settlaghi Ospedale di Circolo e Fondazione Macchi – 21100 Varese - Italy
Brull, Sorin J	Department of Anesthesiology and Perioperative Medicine, College of Medicine, Mayo Clinic Jacksonville, FL, USA
Brunetti, Iole	Anestesia e Terapia Intensiva - IRCCS Policlinico San Martino – Genova – Italy
Bruni, Andrea	Anesthesia and Intensive Care, Department of Medical and Surgical Sciences, Magna Graeca University, Catanzaro, Italy
Buenvenida, Shonie L.	Department of Anesthesiology and Perioperative Medicine, Mayo Clinic, Rochester, Minnesota, USA
Busch, Cornelius Johannes*	Department of Anesthesiology, Heidelberg University Hospital, Im Neuenheimer Feld 110, 69120 Heidelberg, Germany
Camerini, Giovanni	Dipartimento di Scienze Chirurgiche e Diagnostiche Integrate – DISC – Università degli Studi di Genova – Genova – Italy and Clinica Chirurgica 1 - IRCCS Policlinico San Martino – Genova – Italy
Canet, Jaume*	University Hospital Germans Trias i Pujol, ICS, UAB, Spain
Capatti, Beatrice	Department Morphology, Surgery and Experimental Medicine. Anesthesia and intensive care universitary section. University of Ferrara. Italy
Carmona, Javiera	Department of Anesthesiology. School of Medicine. Pontificia Universidad Catolica de Chile
Carungcong, Jaime	Magill Department of Anaesthesia, Chelsea & Westminster NHS Foundation Trust, 369 Fulham Road, London, SW10 9NH, UK
Carvalho, Marta	Serviço de Anestesiologia, Centro Hospitalar do Porto, Porto, Portugal
Cattan, Anat	Division of Anesthesia, Pain and Critical Care, Tel-Aviv Medical Center affiliated with Sackler Medical School, Tel Aviv University, Tel Aviv, Israel
Cavaleiro, Carla	Serviço de Anestesiologia, Centro Hospitalar do Porto, Porto, Portugal and Centro de Investigação Clínica em Anestesiologia, Serviço de Anestesiologia, Centro Hospitalar do Porto, Porto, Portugal
Chiumello, Davide*	Dipartimento di Scienze della Salute, Università degli Studi di Milano, Milan, Italy and SC Anestesia e Rianimazione, ASST Santi Paolo e Carlo, Milan, Italy, Centro ricerca cordinata insufficienza respiratoria
Ciardo, Stefano	Department Morphology, Surgery and Experimental Medicine. Anesthesia and intensive care universitary section. University of Ferrara. Italy
Coburn, Mark	Department of Anesthesiology, Medical Faculty, RWTH Aachen University, Aachen, Germany
Colella, Umberto	Department of Women, child and General and Specialized Surgery. University of Campania "L. Vanvitelli", Italy.
Contreras, Victor	Department of Anesthesiology. School of Medicine. Pontificia Universidad Catolica de Chile
Corman Dincer, Pelin*	Marmara University Pendik Training and Research Hospital, Turkey
Cotter, Elizabeth	Section of Critical Care Medicine, Department of Anesthesia and Critical Care, University of Chicago, Chicago, IL, USA
Crovetto, Marcia	Department of Anesthesiology. School of Medicine. Pontificia Universidad Catolica de Chile
Darrah, William	Department of Anesthesiology, St. Michael's Hospital, University of Toronto, Toronto, ON, Canada
Davies, Simon*	York Teaching Hospitals NHS Foundation Trust, UK
de Baerdemaeker, Luc*	Ghent University Hospital, Ghent, Belgium. Corneel Heymanslaan 10, 9000 Gent, Belgium

De Hert, Stefan	Ghent University Hospital, Ghent, Belgium. Corneel Heymanslaan 10, 9000 Gent, Belgium
Del Cojo Peces, Enrique	Área de Salud Don Benito-Villanueva/Don Benito-Villanueva Health Area, Spain.
Delphin, Ellise	Montefiore Medical Center, Bronx, NY 10467, USA
Diaper, John	Hôpitaux Universitaires de Genève, Département APSI, service d'anesthésiologie, Switzerland
do Nascimento Junior, Paulo*	Department of Anesthesiology, Universidade Estadual Paulista, Botucatu/SP, Brazil
Donatiello, Valerio	Department of Women, child and General and Specialized Surgery. University of Campania "L. Vanvitelli", Italy.
Dong, Jing	Department of Anesthesiology, Fudan University Shanghai Cancer Center, Shanghai, China. Department of Oncology, Shanghai Medical College, Fudan University, Shanghai, China
Dourado, Maria do Socorro	Associação Hospitalar Beneficente São Vicente de Paulo, Brazil
Dullenkopf, Alexander*	Frauenfeld Cantonal Hospital, Switzerland
Ebner, Felix	Klinik für Anästhesiologie, Intensivmedizin und Schmerztherapie,Universitätsklinikum Knappschaftskrankenhaus Bochum, Bochum, Germany
Elgendy, Hamed*	Departments of Anesthesiology, King Abdullah Medical City, Makkah, Saudi Arabia and Assiut University, Egypt and Hamad Medical Corporation, Qatar.
Ellenberger, Christoph	Hôpitaux Universitaires de Genève, Département APSI, service d'anesthésiologie, Switzerland
Erdoğan Arı, Dilek*	Fatih Sultan Mehmet Educational and Research Hospital, İstanbul, Turkey
Ermert, Thomas	Department of Anesthesiology, Intensive Care and Pain Medicine, University Hospital Münster, Münster, Germany
Farah, Fadi	St. Elizabeth's Medical Center, MA, USA
Fernandez-Bustamante, Ana*	University of Colorado School of Medicine, Department of Anesthesiology, CO, USA
Ferreira, Cristina	Serviço de Anestesiologia, Centro Hospitalar do Porto, Porto, Portugal
Fiore, Marco	Department of Women, child and General and Specialized Surgery. University of Campania "L. Vanvitelli", Italy.
Fonte, Ana	Department of Anesthesiology from Centro Hospitalar de Entre o Douro e Vouga, EPE – São Sebastião Hospital, Santa Maria da Feira, Portugal
Fortià Palahí, Christina	Hospital Sagrat Cor- Barcelona, Spain
Galimberti, Andrea	Dipartimento di Scienze della Salute, Università degli Studi di Milano, Milan, Italy and SC Anestesia e Rianimazione, Asst Santi Paolo e Carlo, Milan, Italy, Centro ricerca cordinata insufficienza respiratoria
Gama de Abreu, Marcelo*	Department of Anesthesiology and Intensive Care, Pulmonary Engineering Group, University Hospital Carl Gustav Carus, Technische Universität Dresden, Germany
Garofano, Najia	Hôpitaux Universitaires de Genève, Département APSI, service d'anesthésiologie, Switzerland
Giaccari, Luca Gregorio	Department of Women, child and General and Specialized Surgery. University of Campania "L. Vanvitelli", Italy.
Gilsanz, Fernando	Department of Anesthesiology and Surgical Critical Care, Hospital Universitario La Paz, Madrid, Spain
Girrbach, Felix	Department of Anaesthesiology and Intensive Care Medicine, University of Leipzig, Leipzig, Germany;
Gobbi, Luca	Department Morphology, Surgery and Experimental Medicine. Anesthesia and intensive care universitary section. University of Ferrara. Italy
Godfried,Marc Bernard*	Department of Anesthesiology, Onze Lieve Vrouwe Gasthuis, Amsterdam, The Netherlands

Goettel, Nicolai*	Department of Anesthesia, Surgical Intensive Care, Prehospital Emergency Medicine and Pain Therapy, University Hospital Basel, University of Basel, Basel, Switzerland
Goldstein, Peter A.*	Weill Cornell Medicine, New York, NY, USA
Goren, Or	Division of Anesthesia, Pain and Critical Care, Tel-Aviv Medical Center affiliated with Sackler Medical School, Tel Aviv University, Tel Aviv, Israel
Gorlin, Andrew	Mayo Clinic Arizona, 5777 East Mayo Blvd, Phoenix, AZ, 85054, USA
Granell Gil, Manuel*	Consorcio Hospital General Universitario of Valencia, Spain
Gratarola, Angelo	Anestesia e Rianimazione - IRCCS Policlinico San Martino – Genova – Italy
Graterol, Juan*	Royal Cornwall Hospital NHS Trust, UK
Guyon, Pierre	Hôpitaux Universitaires de Genève, Département APSI, service d'anesthésiologie, Switzerland
Haire, Kevin	Magill Department of Anaesthesia, Chelsea & Westminster NHS Foundation Trust, 369 Fulham Road, London, SW10 9NH, UK
Harou, Philippe	Polyclinique Montier la Celle, France
Helf, Antonia	Department of Anaesthesiology, University Hospital Würzburg, Würzburg, Germany
Hemmes, Sabrine N. T.*	Amsterdam UMC, University of Amsterdam, Department of Anesthesiology, Meibergdreef 9, Amsterdam, The Netherlands
Hempel, Gunther	Department of Anaesthesiology and Intensive Care Medicine, University of Leipzig, Leipzig, Germany;
Hernández Cádiz, María José	Consorcio Hospital General Universitario of Valencia, Spain
Heyse, Björn	Ghent University Hospital, Ghent, Belgium. Corneel Heymanslaan 10, 9000 Gent, Belgium
Hollmann, Markus W.*	Amsterdam UMC, University of Amsterdam, Department of Anesthesiology, Meibergdreef 9, Amsterdam, The Netherlands
Huercio, Ivan	Department of Anesthesiology and Surgical Critical Care, Hospital Universitario La Paz, Madrid, Spain
Ilievska, Jasmina	University Clinic of Surgery “Ss. Naum Ohridski”, Faculty of Medicine, University “Ss. Cyril and Methodius”, Skopje, Macedonia
Jakus, Lien	Hôpitaux Universitaires de Genève, Département APSI, service d'anesthésiologie, Switzerland
Jeganath, Vijay	Royal Stoke University Hospital, UHNM NHS Trust, Stoke-on-Trent, Staffordshire, ST4 6QG, UK
Jelting, Yvonne	Department of Anaesthesiology, University Hospital Würzburg, Würzburg, Germany
Jung, Minoa	Hôpitaux Universitaires de Genève, Département APSI, service d'anesthésiologie, Switzerland
Kabon, Barbara*	Department of Anaesthesia,Critical Care and Pain Medicine, Medical University Vienna, Austria
Kacha, Aalok*	Section of Critical Care Medicine, Department of Anesthesia and Critical Care, University of Chicago, Chicago, IL, USA
Karaman Ilić, Maja	Clinical hospital Sveti Duh, JJ Strossmayer, Faculty of Medicine, Zagreb, Croatia
Karuppiah, Arunthevaraja	St. Elizabeth's Medical Center, MA, USA
Kavas, Ayse Duygu	Marmara University Pendik Training and Research Hospital, Turkey
Keli Barcelos, Gleicy	Hôpitaux Universitaires de Genève, Département APSI, service d'anesthésiologie, Switzerland
Kellogg, Todd A.	Department of Surgery, Mayo Clinic, Rochester, Minnesota, USA
Kemper, Johann	Department of Anesthesiology, University Hospital Duesseldorf, Heinrich-Heine University Duesseldorf, Duesseldorf, Germany
Kerbrat, Romain	Hôpitaux Universitaires de Genève, Département APSI, service d'anesthésiologie, Switzerland
Khodr, Suraya	Cleveland Clinic Abu Dhabi, Al Maryah Island, Abu Dhabi, UAE

Kienbaum, Peter	Department of Anesthesiology, University Hospital Duesseldorf, Heinrich-Heine University Duesseldorf, Duesseldorf, Germany
Kir, Bunyamin	Marmara University Pendik Training and Research Hospital, Turkey
Kiss, Thomas	Department of Anesthesiology and Intensive Care, Pulmonary Engineering Group, University Hospital Carl Gustav Carus, Technische Universität Dresden, Germany
Kivrak, Selin	Hôpitaux Universitaires de Genève, Département APSI, service d'anesthésiologie, Switzerland
Klarić, Vlasta*	Clinic of anesthesiology, reanimatology and intensive care medicine, University Hospital Dubrava, Zagreb, Croatia
Koch, Thea	Department of Anesthesiology and Intensive Care, Pulmonary Engineering Group, University Hospital Carl Gustav Carus, Technische Universität Dresden, Germany
Köksal, Ceren	Fatih Sultan Mehmet Educational and Research Hospital, İstanbul, Turkey
Kowark, Ana	Department of Anesthesiology, Medical Faculty, RWTH Aachen University, Aachen, Germany
Kranke, Peter*	Department of Anaesthesiology, University Hospital Würzburg, Würzburg, Germany
Kuvaki, Bahar*	Dokuz Eylül University Faculty of Medicine, Department of Anaesthesiology and Intensive Care, Turkey
Kuzmanovska, Biljana	University clinic for Traumatology, Orthopedics, Anesthesia, Reanimation, Intensive care and Emmergency center - Skopje, Department of Anesthesiology, Reanimation and Intensive care Medicine - Skopje, Macedonia
Laffey, John*	Department of Anesthesiology, St. Michael's Hospital, University of Toronto, Toronto, ON, Canada
Lange, Mirko	Department of Anaesthesiology and Intensive Care Medicine, University of Leipzig, Leipzig, Germany;
Lemos, Marília Freitas de	Department of Anesthesiology, Hospital do Câncer II, National Cancer Institute of Brazil (INCA), Rio de Janeiro, Brazil
Licker, Marc-Joseph*	Hôpitaux Universitaires de Genève, Département APSI, service d'anesthésiologie; Faculty of Medicine, University of Geneva, Switzerland
López-Baamonde, Manuel	Department of Anaesthesiology, Hospital Clínic, Barcelona, Spain.
López-Hernández, Antonio	Department of Anaesthesiology, Hospital Clínic, Barcelona, Spain.
Lopez-Martinez, Mercedes	Department of Anesthesiology and Surgical Critical Care, Hospital Universitario La Paz, Madrid, Spain
Luise, Stéphane	Hôpitaux Universitaires de Genève, Département APSI, service d'anesthésiologie, Switzerland
MacGregor, Mark*	Ashford and St Peters NHS Foundation Trust, UK
Magalhães, Danielle*	Associação Hospitalar Beneficente São Vicente de Paulo, Brazil
Maillard, Julien	Hôpitaux Universitaires de Genève, Département APSI, service d'anesthésiologie, Switzerland
Malerbi, Patrizia	Anestesia e Rianimazione - IRCCS Policlinico San Martino – Genova – Italy
Manimekalai, Natesan	University of Mississippi Medical Center, MS, USA
Margarson, Michael*	St Richard's Hospital, Chichester, UK
Markstaller, Klaus*	Department of Anaesthesia,Critical Care and Pain Medicine, Medical University Vienna, Austria
Martin, Archer K	Department of Anesthesiology and Perioperative Medicine, College of Medicine, Mayo Clinic Jacksonville, FL, USA
Martin, David P.	Department of Anesthesiology and Perioperative Medicine, Mayo Clinic, Rochester, Minnesota, USA
Martin, Yvette N.	Department of Anesthesiology and Perioperative Medicine, Mayo Clinic, Rochester, Minnesota, USA
Martínez-Ocon, Julia	Department of Anaesthesiology, Hospital Clínic, Barcelona, Spain.

Martin-Loeches, Ignacio*	Department of Intensive Care Medicine, Multidisciplinary Intensive Care Research Organization (MICRO), St. James's Hospital, Dublin, Ireland
Maseda, Emilio	Department of Anesthesiology and Surgical Critical Care, Hospital Universitario La Paz, Madrid, Spain
Matot, Idit*	Division of Anesthesia, Pain and Critical Care, Tel-Aviv Medical Center affiliated with Sackler Medical School, Tel Aviv University, Tel Aviv, Israel
McAuliffe, Niamh	Department of Anesthesiology, St. Michael's Hospital, University of Toronto, Toronto, ON, Canada
McKenzie, Travis J.	Department of Surgery, Mayo Clinic, Rochester, Minnesota, USA
Medina, Paulina	Department of Anesthesiology. School of Medicine. Pontificia Universidad Catolica de Chile
Meersch, Melanie	Department of Anesthesiology, Intensive Care and Pain Medicine, University Hospital Münster, Münster, Germany
Menzen, Angelika*	St. Marienhospital gGmbh Friesoythe, Friesoythe, Germany
Mertens, Els*	University Hospital Antwerp, Belgium
Meurer, Bernd	Marienhospital Wesel, Wesel, Germany
Meyer-Treschan, Tanja*	Department of Anesthesiology, University Hospital Duesseldorf, Heinrich-Heine University Duesseldorf, Duesseldorf, Germany
Miao, Changhong*	Department of Anesthesiology, Fudan University Shanghai Cancer Center, Shanghai, China. Department of Oncology, Shanghai Medical College, Fudan University, Shanghai, China
Micalizzi, Camilla	Dipartimento di Scienze Chirurgiche e Diagnostiche Integrate – DISC – Università degli Studi di Genova – Genova – Italy and Anestesia e Terapia Intensiva - IRCCS Policlinico San Martino – Genova – Italy
Milić, Morena	Clinic of anesthesiology, reanimatology and intensive care medicine, University Hospital Dubrava, Zagreb, Croatia
Módolo, Norma Sueli Pinheiro	Department of Anesthesiology, Universidade Estadual Paulista, Botucatu/SP, Brazil
Moine, Pierre	University of Colorado School of Medicine, Department of Anesthesiology, CO, USA
Mölders, Patrick	Klinik für Anästhesiologie, Intensivmedizin und Schmerztherapie,Universitätsklinikum Knappschaftskrankenhaus Bochum, Bochum, Germany
Montero-Feijoo, Ana	Department of Anesthesiology and Surgical Critical Care, Hospital Universitario La Paz, Madrid, Spain
Moret, Enrique	University Hospital Germans Trias i Pujol, ICS, UAB, Spain
Muller, Markus K.	Frauenfeld Cantonal Hospital, Switzerland
Murphy, Zoe	York Teaching Hospitals NHS Foundation Trust, UK
Nalwaya, Pramod*	Royal Stoke University Hospital, UHNM NHS Trust, Stoke-on-Trent, Staffordshire, ST4 6QG, UK
Naumovski, Filip*	University clinic for Traumatology, Orthopedics, Anesthesia, Reanimation, Intensive care and Emmergency center - Skopje, Department of Anesthesiology, Reanimation and Intensive care Medicine - Skopje, Macedonia
Navalesi, Paolo*	Anesthesia and Intensive Care, Department of Medical and Surgical Sciences, Magna Graeca University, Catanzaro, Italy
Navarro e Lima, Lais Helena	Department of Anesthesiology, Universidade Estadual Paulista, Botucatu/SP, Brazil
Nesek Adam, Višnja*	Clinical hospital Sveti Duh, JJ Strossmayer, Faculty of Medicine, Zagreb, Croatia
Neumann, Claudia	Department of Anaesthesiology and Intensive Care Medicine, University Hospital of Bonn, Bonn, Germany
Newell, Christopher*	Southmead Hospital, North Bristol NHS Trust, UK
Nisnevitch, Zoulfira*	Montefiore Medical Center, Bronx, NY 10467, USA
Nizamuddin, Junaid	Section of Critical Care Medicine, Department of Anesthesia and Critical Care, University of Chicago, Chicago, IL, USA

Novazzi, Cecilia	Universita' dell'Insubria – Dipartimento di Anestesia - Azienda Ospedaliera Asst Settlaghi Ospedale di Circolo e Fondazione Macchi – 21100 Varese - Italy
O'Connor, Michael	Section of Critical Care Medicine, Department of Anesthesia and Critical Care, University of Chicago, Chicago, IL, USA
Oprea, Günther	Klinik für Anästhesiologie, Intensivmedizin und Schmerztherapie, Universitätsklinikum Knappschaftskrankenhaus Bochum, Bochum, Germany
Orhan Sungur, Mukadder	Istanbul University, Istanbul Faculty of Medicine, Turkey
Özbilgin, Şule	Dokuz Eylül University Faculty of Medicine, Department of Anaesthesiology and Intensive Care, Turkey
Pace, Maria Caterina	Department of Women, child and General and Specialized Surgery. University of Campania "L. Vanvitelli", Italy.
Pacheco, Marcos	Department of Anesthesiology from Centro Hospitalar de Entre o Douro e Vouga, EPE – São Sebastião Hospital, Santa Maria da Feira, Portugal
Packianathaswamy, Balaji*	Hull and East Yorkshire Hospitals NHS Trust, UK
Palma Gonzalez, Estefania	Área de Salud Don Benito-Villanueva/Don Benito-Villanueva Health Area, Spain.
Papaspyros, Fotios*	POLYCLINIQUE MONTIER LA CELLE, France
Paredes, Sebastián	Department of Anesthesiology. School of Medicine. Pontificia Universidad Catolica de Chile
Passavanti, Maria Beatrice	Department of Women, child and General and Specialized Surgery. University of Campania "L. Vanvitelli", Italy.
Pedemonte, Juan Cristobal	Department of Anesthesiology. School of Medicine. Pontificia Universidad Catolica de Chile
Pelosi, Paolo*	Dipartimento di Scienze Chirurgiche e Diagnostiche Integrate – DISC – Università degli Studi di Genova – Genova – Italy and Anestesia e Terapia Intensiva - IRCCS Policlinico San Martino – Genova – Italy
Peremin, Sanja	Clinic of anesthesiology, reanimatology and intensive care medicine, University Hospital Dubrava, Zagreb, Croatia
Philipsenburg, Christoph	Department of Anesthesiology, Heidelberg University Hospital, Im Neuenheimer Feld 110, 69120 Heidelberg, Germany
Pinho, Daniela	Serviço de Anestesiologia, Centro Hospitalar do Porto, Porto, Portugal
Pinho, Silvia	Serviço de Anestesiologia, Centro Hospitalar do Porto, Porto, Portugal
Posthuma, Linda M.	Amsterdam UMC, University of Amsterdam, Department of Anesthesiology, Meibergdreef 9, Amsterdam, The Netherlands
Pota, Vincenzo	Department of Women, child and General and Specialized Surgery. University of Campania "L. Vanvitelli", Italy.
Preckel, Benedikt	Amsterdam UMC, University of Amsterdam, Department of Anesthesiology, Meibergdreef 9, Amsterdam, The Netherlands
Priani, Paolo	Department Morphology, Surgery and Experimental Medicine. Anesthesia and intensive care universitary section. University of Ferrara. Italy
Putensen, Christian*	Department of Anaesthesiology and Intensive Care Medicine, University Hospital of Bonn, Bonn, Germany
Rached, Mohamed Aymen	Hôpitaux Universitaires de Genève, Département APSI, service d'anesthésiologie, Switzerland
Radoeshki, Aleksandar	University Clinic of Surgery "Ss. Naum Ohridski", Faculty of Medicine, University "Ss. Cyril and Methodius", Skopje, Macedonia
Ragazzi, Riccardo	Department Morphology, Surgery and Experimental Medicine. Anesthesia and intensive care universitary section. University of Ferrara. Italy
Rajamanickam, Tamilselvan	Royal Stoke University Hospital, UHNM NHS Trust, Stoke-on-Trent, Staffordshire, ST4 6QG, UK

Rajamohan, Arthi	Department of Anesthesiology, St. Michael's Hospital, University of Toronto, Toronto, ON, Canada
Ramakrishna, Harish*	Mayo Clinic Arizona, 5777 East Mayo Blvd, Phoenix, AZ, 85054, USA
Rangarajan, Desikan*	Homerton University Hospitals NHS Foundation Trust, UK
Reiterer, Christian	Department of Anaesthesia,Critical Care and Pain Medicine, Medical University Vienna, Austria
Renew, J. Ross	Department of Anesthesiology and Perioperative Medicine, Mayo Clinic Jacksonville, USA
Reynaud, Thomas	Hôpitaux Universitaires de Genève, Département APSI, service d'anesthésiologie, Switzerland
Rhys, Rhidian	Southmead Hospital, North Bristol NHS Trust, UK
Rivas, Eva*	Department of Anaesthesiology, Hospital Clínic, IDIBAPS, Universitat de Barcelona, Spain
Robitzky, Luisa	Klinik für Anästhesiologie, Intensivmedizin und Schmerztherapie, Universitätsklinikum Knappschaftskrankenhaus Bochum, Bochum, Germany
Rossaint, Rolf*	Department of Anesthesiology, Medical Faculty, RWTH Aachen University, Aachen, Germany
Rubulotta, Francesca*	Imperial College Healthcare NHS Trust, UK
S. Machado, Humberto*	Serviço de Anestesiologia, Centro Hospitalar do Porto, Porto, Portugal and Instituto Ciências Biomédicas Abel Salazar, Universidade do Porto, Porto, Portugal and Centro de Investigação Clínica em Anestesiologia, Serviço de Anestesiologia, Centro Hospitalar do Porto, Porto, Portugal
S. Nunes, Catarina	Universidade Aberta, Departamento de Ciências e Tecnologia, Porto, Portugal and Centro de Investigação Clínica em Anestesiologia, Serviço de Anestesiologia, Centro Hospitalar do Porto, Porto, Portugal
Sabbatini, Giovanni	Dipartimento di Scienze della Salute, Università degli Studi di Milano, Milan, Italy and SC Anestesia e Rianimazione, ASST Santi Paolo e Carlo, Milan, Italy, Centro ricerca cordinata insufficienza respiratoria
Samuels, Jon D	Weill Cornell Medicine, Department of Anesthesiology, New York-Presbyterian Hospital, New York, NY, USA
Sanahuja, Josep Martí	Department of Anaesthesiology, Hospital Clínic, Barcelona, Spain.
Sansone, Pasquale	Department of Women, child and General and Specialized Surgery. University of Campania "L. Vanvitelli", Italy.
Santos, Alice	Department of Anaesthesiology, Centro Hospitalar São João, Porto, Portugal
Sayedalahl, Mohamed	Departments of Anesthesiology, King Abdullah Medical City, Makkah, Saudi Arabia and Mansoura University, Egypt
Schaefer, Maximilian S.	Department of Anesthesiology, University Hospital Duesseldorf, Heinrich-Heine University Duesseldorf, Duesseldorf, Germany
Scharffenberg, Martin	Department of Anesthesiology and Intensive Care, Pulmonary Engineering Group, University Hospital Carl Gustav Carus, Technische Universität Dresden, Germany
Schiffer, Eduardo	Hôpitaux Universitaires de Genève, Département APSI, service d'anesthésiologie; Faculty of Medicine, University of Geneva, Switzerland
Schliewe, Nadja	Department of Anaesthesiology and Intensive Care Medicine, University of Leipzig, Leipzig, Germany;
Schorer, Raoul	Hôpitaux Universitaires de Genève, Département APSI, service d'anesthésiologie, Switzerland
Schultz, Marcus J.	Amsterdam UMC, University of Amsterdam, Department of Anesthesiology, Meibergdreef 9, Amsterdam, The Netherlands
Schumann, Roman	Department of Anesthesiology and Perioperative Medicine, Tufts Medical Center, Boston, MA, USA

Selmo, Gabriele	Universita' dell'Insubria – Dipartimento di Anestesia - Azienda Ospedaliera Asst Settlaghi Ospedale di Circolo e Fondazione Macchi – 21100 Varese - Italy
Sendra, Mar	University Hospital Germans Trias i Pujol, ICS, UAB, Spain
Senturk, Mert*	Istanbul University, Istanbul Faculty of Medicine, Turkey
Severgnini, Paolo*	Universita' dell'Insubria – Dipartimento di Anestesia - Azienda Ospedaliera Asst Settlaghi Ospedale di Circolo e Fondazione Macchi – 21100 Varese - Italy
Shaw, Kate	York Teaching Hospitals NHS Foundation Trust, UK
Shosholcheva, Mirjana*	University Clinic of Surgery "Ss. Naum Ohridski", Faculty of Medicine, University "Ss. Cyril and Methodius", Skopje, Macedonia
Sibai, Abdulrazak*	MINISTRY OF NATIONAL GUARD HEALTH AFFAIRS, KING ABDULAZIZ MEDICAL CITY – RIYADH, Anesthesia Department, Saudi Arabia
Simon, Philipp	Department of Anaesthesiology and Intensive Care Medicine, University of Leipzig, Leipzig, Germany;
Simonassi, Francesca	Dipartimento di Scienze Chirurgiche e Diagnostiche Integrate – DISC – Università degli Studi di Genova – Genova – Italy and Anestesia e Terapia Intensiva - IRCCS Policlinico San Martino – Genova – Italy
Sinno, Claudia	Universita' dell'Insubria – Dipartimento di Anestesia - Azienda Ospedaliera Asst Settlaghi Ospedale di Circolo e Fondazione Macchi – 21100 Varese - Italy
Sivrikoz, Nukhet	Istanbul University, Istanbul Faculty of Medicine, Turkey
Skandalou, Vasiliki*	Alexandra General Hospital, Athens, Greece
Smith, Neil	Hull and East Yorkshire Hospitals NHS Trust, UK
Soares, Maria	Serviço de Anestesiologia, Centro Hospitalar do Porto, Porto, Portugal
Socorro Artiles, Tania	University Clinic Hospital Valencia, Spain
Sousa Castro, Diogo*	Department of Anesthesiology from Centro Hospitalar de Entre o Douro e Vouga, EPE – São Sebastião Hospital, Santa Maria da Feira, Portugal
Sousa, Miguel	Department of Anesthesiology from Centro Hospitalar de Entre o Douro e Vouga, EPE – São Sebastião Hospital, Santa Maria da Feira, Portugal
Spadaro, Savino*	Department Morphology, Surgery and Experimental Medicine. Anesthesia and intensive care universitary section. University of Ferrara. Italy
Sprung, Juraj*	Department of Anesthesiology and Perioperative Medicine, Mayo Clinic, Rochester, Minnesota, USA
Stamatakis, Emmanouil	Alexandra General Hospital, Athens, Greece
Steiner, Luzius A.	Department of Anesthesia, Surgical Intensive Care, Prehospital Emergency Medicine and Pain Therapy, University Hospital Basel, University of Basel, Basel, Switzerland
Stevenazzi, Andrea	University Hospital Germans Trias i Pujol, ICS, UAB, Spain
Suarez-de-la-Rica, Alejandro*	Department of Anesthesiology and Surgical Critical Care, Hospital Universitario La Paz, Madrid, Spain
Suppan, Mélanie	Hôpitaux Universitaires de Genève, Département APSI, service d'anesthésiologie, Switzerland
Teichmann, Robert	Department of Anesthesiology and Intensive Care, Pulmonary Engineering Group, University Hospital Carl Gustav Carus, Technische Universität Dresden, Germany
Tena Guerrero, José Maria*	Área de Salud Don Benito-Villanueva/Don Benito-Villanueva Health Area, Spain.
Thiel, Bram	Department of Anesthesiology, Onze Lieve Vrouwe Gasthuis, Amsterdam, The Netherlands
Tolós, Raquel	University Hospital Germans Trias i Pujol, ICS, UAB, Spain

Tore Altun, Gulbin	Marmara University Pendik Training and Research Hospital, Turkey
Tucci, Michelle	University of Mississippi Medical Center, MS, USA
Turnbull, Zachary A.	Weill Cornell Medicine, New York, NY, USA
Turudić, Žana	Clinic of anesthesiology, reanimatology and intensive care medicine, University Hospital Dubrava, Zagreb, Croatia
Unterberg, Matthias	Klinik für Anästhesiologie, Intensivmedizin und Schmerztherapie, Universitätsklinikum Knappschaftskrankenhaus Bochum, Bochum, Germany
Van Limmen, Jurgen	Ghent University Hospital, Ghent, Belgium. Corneel Heymanslaan 10, 9000 Gent, Belgium
Van Nieuwenhove, Yves	Ghent University Hospital, Ghent, Belgium. Corneel Heymanslaan 10, 9000 Gent, Belgium
Van Waesberghe, Julia	Department of Anesthesiology, Medical Faculty, RWTH Aachen University, Aachen, Germany
Vidal Melo, Marcos Francisco*	Department of Anesthesia, Critical Care and Pain Medicine, Massachusetts General Hospital, Boston, Massachusetts, USA
Vitković, Bibiana	Clinic of anesthesiology, reanimatology and intensive care medicine, University Hospital Dubrava, Zagreb, Croatia
Vivona, Luigi	Department of Anesthesiology and Intensive Care, Pulmonary Engineering Group, University Hospital Carl Gustav Carus, Technische Universität Dresden, Germany
Vizcaychipi, Marcela*	Magill Department of Anaesthesia, Chelsea & Westminster NHS Foundation Trust, 369 Fulham Road, London, SW10 9NH, UK
Volta, Carlo Alberto	Department Morphology, Surgery and Experimental Medicine. Anesthesia and intensive care universitary section. University of Ferrara. Italy
Weber, Anne	Hôpitaux Universitaires de Genève, Département APSI, service d'anesthésiologie, Switzerland
Weingarten, Toby N.	Department of Anesthesiology and Perioperative Medicine, Mayo Clinic, Rochester, Minnesota, USA
Wittenstein, Jakob	Department of Anesthesiology and Intensive Care, Pulmonary Engineering Group, University Hospital Carl Gustav Carus, Technische Universität Dresden, Germany
Wrigge, Hermann*	Department of Anaesthesiology and Intensive Care Medicine, University of Leipzig, Leipzig, Germany and Department of Anaesthesiology, Intensive Care and Emergency Medicine, Pain Therapy; Bergmannstrost Hospital Halle, Halle, Germany
Wyffels, Piet	Ghent University Hospital, Ghent, Belgium. Corneel Heymanslaan 10, 9000 Gent, Belgium
Yagüe, Julio	Department of Anesthesiology and Surgical Critical Care, Hospital Universitario La Paz, Madrid, Spain
Yates, David	York Teaching Hospitals NHS Foundation Trust, UK
Yavru, Ayşen	Istanbul University, Istanbul Faculty of Medicine, Turkey
Zac, Lilach	Division of Anesthesia, Pain and Critical Care, Tel-Aviv Medical Center affiliated with Sackler Medical School, Tel Aviv University, Tel Aviv, Israel
Zhong, Jing	Department of Anesthesiology, Fudan University Shanghai Cancer Center, Shanghai, China. Department of Oncology, Shanghai Medical College, Fudan University, Shanghai, China

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Respiration and the Airway

RESPIRATION AND THE AIRWAY

Intraoperative positive end-expiratory pressure and postoperative pulmonary complications: a patient-level meta-analysis of three randomised clinical trials

Niklas S. Campos[1,2,†], Thomas Bluth[3], Sabrine N. T. Hemmes[4,5], Julian Librero[6], Natividad Pozo[7], Carlos Ferrando[8,9], Lorenzo Ball[10], Guido Mazzinari[11,12], Paolo Pelosi[10], Marcelo Gama de Abreu[3], Marcus J. Schultz[4,13,14,15], A. Serpa Neto[1,2,4,16,17,†,*], and for the REPEAT[‡], investigators for the PROVHILO study, the iPROVE study, the PROBESE study investigators, the PROVE Network

[1]Department of Critical Care Medicine, Hospital Israelita Albert Einstein, Sao Paulo, Brazil, [2]Cardio-Pulmonary Department, Pulmonary Division, Faculdade de Medicina, Instituto do Coração, Hospital das Clinicas HCFMUSP, Universidade de Sao Paulo, Sao Paulo, Brazil, [3]Pulmonary Engineering Group, Department of Anesthesiology and Intensive Care Medicine, University Hospital Carl Gustav Carus, Technische Universität Dresden, Dresden, Germany, [4]Department of Intensive Care, Amsterdam University Medical Centers, location 'AMC', Amsterdam, the Netherlands, [5]Department of Anesthesiology, Amsterdam University Medical Centers, location 'AMC', Amsterdam, the Netherlands, [6]Navarrabiomed-Fundación Miguel Servet, Red de Investigación en Servicios de Salud en Enfermedades Crónicas (REDISSEC), Pamplona, Spain, [7]INCLIVA Clinical Research Institute, Hospital Clinico Universitario de Valencia, Valencia, Spain, [8]Department of Anesthesiology & Critical Care, Hospital Clinico Universitario de Valencia, Valencia, Spain, [9]CIBER de Enfermedades Respiratorias, Instituto de Salud Carlos III, Madrid, Spain, [10]Department of Surgical Sciences and Integrated Diagnostics, San Martino Policlinico Hospital – IRCCS for Oncology, University of Genoa, Genoa, Italy, [11]Research Group in Perioperative Medicine, Hospital Universitario y Politécnico la Fe, Valencia, Spain, [12]Department of Anesthesiology, Hospital Universitario y Politécnico la Fe, Valencia, Spain, [13]Laboratory of Experimental Intensive Care and Anesthesiology (LEICA), Amsterdam University Medical Centers, location 'AMC', Amsterdam, the Netherlands, [14]Nuffield Department of Medicine, University of Oxford, Oxford, UK, [15]Mahidol Oxford Research Unit (MORU), Mahidol University, Bangkok, Thailand, [16]Australian and New Zealand Intensive Care Research Centre (ANZIC-RC), Monash University, Melbourne, Australia and [17]Department of Critical Care, Melbourne Medical School, University of Melbourne, Austin Hospital, Melbourne, Australia

*Corresponding author. E-mail: ary.neto2@einstein.br

[†]N.S. Campos and A.S. Neto contributed equally to the work.
[‡]Names and affiliations of REPEAT collaborators are listed in the Appendix.

Abstract

Background: High intraoperative PEEP with recruitment manoeuvres may improve perioperative outcomes. We re-examined this question by conducting a patient-level meta-analysis of three clinical trials in adult patients at increased risk for postoperative pulmonary complications who underwent non-cardiothoracic and non-neurological surgery.

Methods: The three trials enrolled patients at 128 hospitals in 24 countries from February 2011 to February 2018. All patients received volume-controlled ventilation with low tidal volume. Analyses were performed using one-stage,

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two-level, mixed modelling (site as a random effect; trial as a fixed effect). The primary outcome was a composite of postoperative pulmonary complications within the first week, analysed using mixed-effect logistic regression. Pre-specified subgroup analyses of nine patient characteristics and seven procedure and care-delivery characteristics were also performed.

Results: Complete datasets were available for 1913 participants ventilated with high PEEP and recruitment manoeuvres, compared with 1924 participants who received low PEEP. The primary outcome occurred in 562/1913 (29.4%) participants randomised to high PEEP, compared with 620/1924 (32.2%) participants randomised to low PEEP (unadjusted odds ratio [OR]=0.87; 95% confidence interval [95% CI], 0.75–1.01; P=0.06). Higher PEEP resulted in 87/1913 (4.5%) participants requiring interventions for desaturation, compared with 216/1924 (11.2%) participants randomised to low PEEP (OR=0.34; 95% CI, 0.26–0.45). Intraoperative hypotension was associated more frequently (784/1913 [41.0%]) with high PEEP, compared with low PEEP (579/1924 [30.1%]; OR=1.87; 95% CI, 1.60–2.17).

Conclusions: High PEEP combined with recruitment manoeuvres during low tidal volume ventilation in patients undergoing major surgery did not reduce postoperative pulmonary complications.

Clinical trial registration: NCT03937375 (Clinicaltrials.gov).

Keywords: mechanical ventilation; PEEP; postoperative pulmonary complications; surgery

Editor's key points

- The putative benefits of high intraoperative PEEP with recruitment manoeuvres remain unclear.
- This patient-level meta-analysis examined whether postoperative pulmonary complications within the first week after surgery were reduced by high intraoperative PEEP.
- Heterogeneous outcome measures hampered the interpretation of the trials.
- High intraoperative PEEP was associated with fewer episodes of desaturation but more frequent intraoperative hypotension.
- High intraoperative PEEP with recruitment manoeuvres during low tidal volume ventilation does not reduce postoperative pulmonary complications.

Postoperative pulmonary complications occur frequently, and are associated with longer hospital length of stay, higher costs, and increased mortality.[1–3] Intraoperative low tidal volume potentially protects against postoperative pulmonary complications.[4–6] In contrast, the protective role of high PEEP with recruitment manoeuvres is less certain, as in most studies high PEEP with recruitment manoeuvres was combined with a low tidal volume, whereas in the control arm low PEEP was combined with a high tidal volume.

Higher tidal volumes during surgery is a contributing factor to the development of postoperative pulmonary complications, which obscures any potential effects of PEEP.[4–7] Although high PEEP with recruitment manoeuvres can protect the lungs against repetitive tidal recruitment and reduce the risk for intraoperative hypoxaemia, high PEEP may also cause overdistension and increase the risk for intraoperative hypotension.[7 8]

The results of three large multicentre, randomised clinical trials (PROVHILO [Protective ventilation during general anaesthesia for open abdominal surgery], iPROVE [Individualized perioperative open lung ventilatory strategy], and PROBESE [Protective intraoperative ventilation in obese patients]) appear to argue against the preventive use of high PEEP with recruitment manoeuvres in surgical patients at risk for postoperative pulmonary complications.[9–11] However, as there was significant heterogeneity amongst patients in these trials, and differences in usual care across participating hospitals, treatment effects in certain subgroups or particular settings cannot be ruled out. We therefore undertook an individual patient-level meta-analysis to examine whether high PEEP with recruitment manoeuvres may reduce postoperative pulmonary complications and adverse intraoperative events, compared with patients randomised to low PEEP.

Methods

This study was registered at Clinicaltrials.gov (NCT03937375). The protocol and statistical analysis plan of this meta-analysis were published before data pooling and start of the analysis.[12] The investigators of each trial provided the study protocols, case-report forms, and data dictionaries, which were compared for recoding if necessary. After receipt of the individual patient data, values were checked for missing and consistency, and data queries were sent to the investigators whenever needed. (Supplementary Table S1).

Original trial characteristics

The three original trials evaluated the effects of intraoperative high PEEP with recruitment manoeuvres on postoperative outcomes, with similar intraoperative care (Table 1).[9–11] Participation in the original studies required written informed consent and adhered to Good Clinical Practice.

Inclusion and exclusion criteria

No additional inclusion or exclusion criteria were used for this meta-analysis. The common inclusion criteria used in each trial were: (1) age ≥18 yr, (2) major surgery, and (3) Assess Respiratory Risk in Surgical Patients in Catalonia (ARISCAT) score ≥26 (Table 1).

Primary outcome

The primary outcome was the proportion of patients developing one or more postoperative pulmonary complications within the first 7 postoperative days, defined as a collapsed composite of mild and severe respiratory failure (according to Pao_2 and SpO_2, and the degree of respiratory support), acute

Table 1 Characteristics of the included trials. *Based on the Cochrane risk of bias tool. ARDS, acute respiratory distress syndrome; ARISCAT, Assess Respiratory Risk in Surgical Patients in Catalonia; ARR, absolute risk reduction; Cdyn, dynamic compliance; COPD, chronic obstructive pulmonary disease; iPROVE, individualized perioperative open lung ventilatory strategy; NIV, noninvasive ventilation; OLV, one-lung ventilation; PAH, pulmonary arterial hypertension; PBW, predicted body weight; PEPC, postoperative extrapulmonary complications; PPC, postoperative pulmonary complications; PROBESE, protective intraoperative ventilation in obese patients; PROVHILO, protective ventilation during general anaesthesia for open abdominal surgery; VCV, volume-controlled ventilation; VF, ventilatory frequency.

	PROVHILO	iPROVE	PROBESE
General			
Number of centres	30	21	77
Countries	International	Spain	International
Eligibility			
Inclusion criteria	1. Age ≥18 yr 2. Open abdominal surgery 3. ARISCAT ≥26	1. Age ≥18 yr 2. Major abdominal surgery 3. ARISCAT ≥26 4. Expected duration >2 h	1. Age ≥18 yr 2. Major surgery 3. ARISCAT ≥ 26 4. Expected duration >2 h 5. BMI ≥35 kg m^{-2}
Exclusion criteria	1. Laparoscopic surgery 2. BMI >40 kg m^{-2} 3. Pregnancy 4. Previous lung surgery 5. COPD with NIV or oxygen 6. Use of ventilation <30 days 7. ARDS 8. Intractable shock 9. Severe cardiac disease 10. Immunosuppression <60 days	1. BMI ≥35 kg m^{-2} 2. Pregnancy 3. Intracranial hypertension 4. Pneumothorax or giant bullae 5. COPD with NIV or oxygen 6. Use of ventilation <15 days 7. Moderate or severe ARDS 8. Heart failure	1. Neurosurgery or cardiac surgery 2. Need of OLV 3. Planned reintubation after surgery 4. Prone or lateral positioning 5. Pregnancy 6. Previous lung surgery 7. COPD with NIV or oxygen 8. Use of ventilation <30 days 9. Intractable shock 10. Severe cardiac disease 11. Immunosuppression <60 days 12. Severe PAH 13. Neuromuscular disease 14. Intracranial tumour or injury
Number of patients	894	967	1976
Outcome			
Primary	1. Incidence of PPC	1. Incidence of pulmonary and systemic complications	1. Incidence of PPC
Secondary	1. Intraoperative complications 2. Unexpected ICU admission 3. Hospital-free days at day 90 4. Postoperative wound healing 5. PEPC 6. Mortality	1. ICU length of stay 2. Hospital length of stay 3. ICU readmission 4. Hospital readmission 5. Mortality	1. Incidence of severe PPC 1. Intraoperative complications 2. Unexpected ICU admission 3. Hospital-free days at day 90 4. Postoperative wound healing 5. PEPC 6. Mortality
Intervention			
High PEEP arm	1. Mode: VCV 2. Tidal volume ≤8 ml kg PBW^{-1} 3. FiO_2 >0.40 to SpO_2 ≥92% 4. PEEP at 12 cm H_2O 5. Recruitment manoeuvres (directly after induction of anaesthesia, after any disconnection from the ventilator, and just before tracheal extubation) 6. I:E at 1:2 7. VF to $etco_2$ 4.5–6.0 kPa	1. Mode: VCV 2. Tidal volume ≤8 ml kg^{-1} PBW 3. FiO_2 of 0.80 4. PEEP titrated by C_{dyn} 5. Recruitment manoeuvres (after intubation, and if respiratory system compliance decreased more than 10% and SpO_2 decreased to 96% or lower) 6. I:E at 1:2 7. VF to $etco_2$ 4.5–6.0 kPa	1. Mode: VCV 2. Tidal volume ≤7 ml kg^{-1} PBW 3. FiO_2 ≥0.40 to SpO_2 ≥92% 4. PEEP at 12 cm H_2O 5. Recruitment manoeuvres (after endotracheal intubation, repeated every hour after any disconnection from the mechanical ventilator, and before the end of surgery) 6. I:E at 1:2 7. VF to $etco_2$ 4.5–6.0 kPa

Continued

Table 1 Continued

	PROVHILO	iPROVE	PROBESE
Low PEEP arm	1. Mode: VCV 2. Tidal volume ≤8 ml kg^{-1} PBW 3. FiO_2 >0.40 to SpO_2 ≥92% 4. PEEP ≤2 cm H_2O 5. No recruitment manoeuvres 6. I:E at 1:2 7. VF to $etco_2$ 4.5–6.0 kPa	1. Mode: VCV 2. Tidal volume ≤8 ml kg^{-1} PBW 3. FiO_2 of 0.80 4. PEEP at 5 cm H_2O 5. No recruitment manoeuvres 6. I:E at 1:2 7. VF to $etco_2$ 4.5–6.0 kPa	1. Mode: VCV 2. Tidal volume ≤7 ml kg^{-1} PBW 3. FiO_2 >0.40 to SpO_2 ≥92% 4. PEEP at 4 cm H_2O 5. No recruitment manoeuvres 6. I:E at 1:2 7. VF to $etco_2$ 4.5–6.0 kPa
Sample size			
Power	80%	80%	80%
Effect size	7.5% ARR	12.5% ARR	10% ARR
Incidence in control	24%	25%	20%
Alpha	Two-sided 0.05	Two-sided 0•05	Two-sided 0•05
Interim analyses	Two at 300 and 600	Two at 460 and 600	Two at 50% and 75%
Stopping rules	O'Brien–Fleming	Modified Haybittle–Peto	Lan–DeMets alpha-spending function
Randomisation			
Sequence generation	Patient-level, permuted block randomisation with variable block sizes and stratified by centre	Patient-level, permuted block randomisation with variable block sizes	Patient-level, permuted block randomisation with variable block sizes and stratified by centre
Allocation concealment	Central Web-based, accessible 24 h day^{-1}	Central Web-based, accessible 24 h day^{-1}	Central Web-based, accessible 24 h day^{-1}
Blinding			
Methods	Double blinded with one investigator applying the intraoperative intervention and other doing the follow-up	Double blinded with one investigator applying the intraoperative intervention and other doing the follow-up	Double blinded with one investigator applying the intraoperative intervention and other doing the follow-up
Statistical methods			
Methods	Intention-to-treat	Modified intention-to-treat	Modified intention-to-treat
*Risk of bias**			
Random sequence generation	Low risk of bias	Low risk of bias	Low risk of bias
Allocation concealment	Low risk of bias	Low risk of bias	Low risk of bias
Blinding of participants and personnel	High risk of bias	High risk of bias	High risk of bias
Blinding of outcome assessment	Low risk of bias	Low risk of bias	Low risk of bias
Incomplete outcome data	Low risk of bias	Low risk of bias	Low risk of bias
Selective reporting	Low risk of bias	Low risk of bias	Low risk of bias
Other source of bias	Low risk of bias	Low risk of bias	Low risk of bias

Table 2 Study participant characteristics. Data are mean (standard deviation), median (quartile 25–75) or *n* (%). *The Assess Respiratory Risk in Surgical Patients in Catalonia (ARISCAT) score estimates the risk of postoperative pulmonary complications, with scores greater or equal than 45 indicating high risk. †Defined as haemoglobin ≤10 g dl^{-1}. ‡The ASA criteria for physical status include a classification for normal health (1), mild systemic disease (2), severe systemic disease (3), severe systemic disease that is a constant threat to life (4), and a moribund person who is not expected to survive without the operation (6). PPC, postoperative pulmonary complications.

	High PEEP (*n*=1913)	Low PEEP (*n*=1924)
Age (yr)	55.9 (15.6)	56.8 (15.3)
Range	(19–93)	(18–91)
Female sex	1058/1910 (55.4)	1046/1918 (54.5)
Height (cm)	166 (10)	166 (9)
Weight (kg)	96.3 (31.9)	95.0 (30.9)
BMI (kg m^{-2})	34.5 (10.7)	34.2 (10.5)
<30	756/1758 (43.0)	783/1761 (44.5)
30–35	143/1758 (8.1)	116/1761 (6.6)
≥35	859/1758 (48.9)	862/1761 (48.9)
ARISCAT score*	36.9 (9.6)	37.1 (9.7)
Intermediate	1604/1900 (84.0)	1586/1912 (82.5)
High	306/1900 (16.0)	336/1912 (17.5)
Risk factors for PPC		
SpO_2 (%)	97 (2)	97 (2)
≥96	1430/1898 (75.3)	1394/1905 (73.2)
91–95	452/1898 (23.8)	497/1905 (26.1)
<91	16/1898 (0.8)	14/1905 (0.7)
Respiratory infection within the past month	111/1903 (5.8)	94/1914 (4.9)
Anaemia†	123/1720 (7.2)	120/1732 (6.9)
Surgical incision		
Peripheral	126 (6.6)	126 (6.5)
Abdominal	1787 (93.4)	1798 (93.5)
Emergency procedure	30 (1.6)	28 (1.5)
ASA physical status‡		
1	101/1896 (5.3)	108/1903 (5.7)
2	972/1896 (51.3)	933/1903 (49.0)
3	808/1896 (42.6)	841/1903 (44.2)
4	14/1896 (0.7)	21/1903 (1.1)
5	1/1896 (0.1)	0/1903 (0.0)
Coexisting conditions		
Heart failure	133/1902 (7.0)	151/1914 (7.9)
Chronic obstructive pulmonary disease	113/1912 (5.9)	109/1923 (5.7)
Cancer	783/1906 (41.1)	817/1921 (42.5)
Preoperative haemoglobin (g dl^{-1})	13.2 (2.0)	13.2 (2.0)
Type of surgery		
Abdominal	1819/1911 (95.2)	1821/1923 (94.7)
Non-abdominal	92/1911 (4.8)	102/1923 (5.3)
Specific procedure		
Bariatric	557/1911 (29.1)	562/1923 (29.2)
Bladder or urology	107/1911 (5.6)	106/1923 (5.5)
Bowel	21/1911 (1.1)	27/1923 (1.4)
Colorectal	390/1911 (20.4)	384/1923 (20.0)
Gastric	106/1911 (5.5)	109/1923 (5.7)
Hepatic	170/1911 (8.9)	149/1923 (7.7)
Hernia	31/1911 (1.6)	32/1923 (1.7)
Kidney	20/1911 (1.0)	32/1923 (1.7)
Pancreatic	110/1911 (5.8)	120/1923 (6.2)
Gynaecology	91/1911 (4.8)	91/1923 (4.7)
Head and neck	24/1911 (1.3)	24/1923 (1.2)
Orthopaedic	35/1911 (1.8)	29/1923 (1.5)
Plastic	9/1911 (0.5)	23/1923 (1.2)
Vascular	35/1911 (1.8)	35/1923 (1.8)
Other gynaecology	10/1911 (0.5)	9/1923 (0.5)
Other urology	3/1911 (0.2)	4/1923 (0.2)
Others	192/1911 (10.0)	187/1923 (9.7)
Surgical approach		
Non-laparoscopic	870/1779 (48.9)	874/1782 (49.0)
Laparoscopic	909/1779 (51.1)	908/1782 (51.0)

respiratory distress syndrome (according to Berlin definition), pulmonary infection (according to a combined criteria of chest X-ray, fever white blood cell count and sputum), pleural effusion (according to chest radiography), atelectasis (according to chest radiography), pneumothorax (according to chest radiography), and bronchospasm (according to the presence of wheezing and use of bronchodilator). Details on individual components of the composite are shown in Supplementary Table S2g.

Secondary outcomes

Secondary outcomes included intraoperative complications including rescue for desaturation and hypotension; 'severe' postoperative pulmonary complications in which mild respiratory failure was ignored; and 'major postoperative complications', a composite consisting of 'severe' postoperative pulmonary complications, postoperative sepsis or septic shock and postoperative acute kidney injury. Unexpected need for ICU admission, hospital length of stay, 7-day mortality, and in-hospital mortality were additional secondary endpoints.

Statistical analyses

All analyses were conducted on an intention-to-treat basis (according to the original group allocation in the original trials) and performed using one stage, two-level (patients nested in study sites, within the trials), mixed modelling with site as random effect and trial as a fixed effect. Heterogeneity between trials was determined by fitting a fixed interaction term between treatment and trial, whereas overall treatment effect is reported with trial treated as a fixed effect and site treated as a random effect. The primary outcome (and other binary outcomes) was analysed using mixed-effect logistic regression and reported as odds ratio and 95% confidence intervals (CIs). Hospital length of stay was analysed with mixed-effect generalised linear models considering an inverse Gaussian distribution (according to best fit) and reported as mean difference and 95% CI. Analyses were not adjusted for strong prognostic covariates.

To determine if the relationship between treatment and the primary outcome differs between pre-specified, clinically important subgroups, fixed interaction terms between treatment and subgroup were added in the unadjusted model for the primary outcome described above. To further ascertain if the treatment–subgroup interaction varied between the three studies, a three-way fixed interaction between trial, treatment, and subgroup were also reported. Pre-specified subgroups according to baseline patient characteristics were age, gender, BMI, baseline SpO_2, surgical risk (ASA physical status, ranging from 1 to 5 with higher scores indicating greater surgical risk), risk for postoperative pulmonary complications (ARISCAT score, ranging from 0 to 123 with higher scores indicating greater risk), chronic obstructive pulmonary disease, cancer and preoperative anaemia. Pre-specified subgroups according to procedure and intervention characteristics were type of procedure (non-laparoscopic or laparoscopic), surgical site (abdominal or non-abdominal), urgency of surgery (emergency or non-emergency), type of PEEP selection (fixed or titrated), and use of postoperative intervention. Finally, pre-specified subgroups according to care-delivery factors were day of start of anaesthesia (weekday or weekend) and time of start of anaesthesia (day or night).

As sensitivity analyses, the effect of the intervention on the primary and secondary outcomes were re-estimated using the same mixed-effect models described above but adjusted for pre-specified baseline covariates of sex (included as a categorical variable), age, baseline SpO_2, ARISCAT score, and BMI (included as continuous variables). Because the primary outcome was a composite outcome, additional sensitivity analyses were also performed (described in detail in Supplement 1). The following analyses were performed: (1) a count analysis (the number of positive component events, i.e. 'count' across the composite); (2) an individual component analysis (the effect of the intervention on each component of the composite); (3) a common effect test (estimation of the common effect odds ratio across the individual components of the composite); (4) an average relative effect test (estimation of a distinct treatment effect for each component of the composite); and (5) a heterogeneity of treatment effect (estimation of heterogeneity of treatment effect across components of the composite). A *post-hoc* sensitivity analysis was performed assessing the impact of the intervention on the primary outcome after adjustment for sex, emergency procedure, need of vasopressor (as categorical variables), age, baseline SpO_2, ARISCAT score, BMI, duration of surgery, blood loss, and total fluid intake (as continuous variables).

All analyses were performed using the R (R, version 3.6.0; Core Team, Vienna, Austria, 2016) software, and a two-sided alpha level of 0.05 was considered. Complete-case analysis was used for all outcomes because data were missing for less than 1% for all outcomes. In addition to the unadjusted *P*-values for secondary outcomes, a Holm–Bonferroni procedure was applied to control the family-wide error rate to the *P* values for all 14 secondary outcomes. The subgroup analyses were not adjusted for multiple comparisons; with 16 pre-specified subgroup analyses, one significant interaction test would be expected by chance alone.

Results

Participant characteristics

From February 2011 through February 2018, the three original studies enrolled 3925 patients at 128 hospitals in 24 countries worldwide with 3837 patients eligible for inclusion in the patient-level meta-analysis. Overall, 1913 patients received high PEEP and recruitment manoeuvres (high PEEP), compared with 1924 patients who received low PEEP (low PEEP). (Table 2; Supplementary Tables S3 and S4). Intraoperative characteristics were similar between participants randomised to high *vs* low PEEP (Table 3). Peak pressure was higher and driving pressure was lower in the high PEEP group (Supplementary Fig. S5). Recruitment manoeuvres were almost universal in the high PEEP group, compared with <0.5% in the low PEEP group (Supplementary Fig. S5). Additional cardiorespiratory data are provided in supplementary data (Supplementary Figs S6 and S7). Postoperative pulmonary complications occurred most commonly (93%) within in the first 3 days after surgery.

Primary outcome: pulmonary morbidity after surgery

One or more postoperative pulmonary complications within the first 7 days after surgery (Table 4) occurred in 562/1913

Table 3 Intraoperative management. Data are mean (standard deviation), median (quartile 25–75) or *n* (%). *Unless when indicated, absolute difference is the mean difference calculated from a mixed-effect linear model with trials as fixed effect and sites as random effect. †Any recruitment during surgery. In iPROVE, protocol mandated only one recruitment manoeuvre after intubation. ‡Absolute difference is the risk difference calculated from a mixed-effect generalised linear model considering a binomial distribution with an identity link and with trials as fixed effect and sites as random effect. ¶Driving pressure calculated as plateau pressure − PEEP. §Calculated as the difference in the use of balanced anaesthesia. FiO_2, inspired fraction of oxygen; SpO_2, pulse oximetry; $ETco_2$, partial end-tidal carbon dioxide.

	High PEEP ($n = 1913$)	Low PEEP ($n = 1924$)	Absolute difference* (95% CI)	*P*-value
Tidal volume (ml kg^{-1} PBW)				
After induction	7.6 (1.3)	7.6 (0.9)	0.03 (−0.04 to 0.09)	0.41
First hour	7.7 (1.3)	7.6 (0.7)	0.07 (0.01–0.13)	0.02
Last hour	7.7 (1.5)	7.6 (0.8)	0.09 (0.02–0.16)	0.008
PEEP (cm H_2O)				
After induction	10.7 (3.3)	3.2 (1.7)	7.51 (7.37–7.66)	<0.001
First hour	11.5 (2.0)	3.8 (1.8)	7.73 (7.62–7.84)	<0.001
Last hour	11.5 (2.2)	3.8 (1.9)	7.72 (7.60–7.84)	<0.001
Recruitment manoeuvres†				
After induction	1885 (98.5)	6 (0.3)	98.20 (97.62–98.75)‡	<0.001
First hour	1329 (69.5)	8 (0.4)	69.12 (67.51–70.74)‡	<0.001
Last hour	1402 (73.3)	7 (0.4)	72.96 (71.48–74.44)‡	<0.001
Number − median (IQR)	3 (1–4)	0 (0–0)	3.18 (3.11–3.25)	<0.001
Peak pressure (cm H_2O)				
After induction	23.3 (5.7)	20.9 (6.1)	2.33 (2.02–2.63)	<0.001
First hour	26.2 (5.6)	23.4 (6.8)	2.81 (2.49–3.12)	<0.001
Last hour	25.6 (5.4)	22.7 (6.5)	2.88 (2.58–3.18)	<0.001
Driving pressure¶ (cm H_2O)				
After induction	11.3 (4.6)	15.4 (5.1)	−4.15 (−4.57 to −3.73)	<0.001
First hour	11.8 (4.5)	16.4 (5.7)	−4.68 (−5.03 to −4.33)	<0.001
Last hour	11.0 (4.8)	15.4 (5.7)	−4.46 (−4.80 to −4.11)	<0.001
Ventilatory frequency (bpm)				
After induction	12.9 (2.7)	13.2 (2.6)	−0.29 (−0.42 to −0.17)	<0.001
First hour	14.0 (3.5)	14.2 (3.5)	−0.19 (−0.33 to −0.05)	0.007
Last hour	14.8 (4.0)	15.0 (4.1)	−0.19 (−0.35 to −0.02)	0.02
FiO_2 (%)				
After induction	64.4 (21.9)	63.7 (21.3)	0.83 (−0.02 to 1.68)	0.05
First hour	53.7 (16.9)	55.3 (16.9)	−1.59 (−2.13 to −1.05)	<0.001
Last hour	54.0 (17.6)	56.5 (18.3)	−2.60 (−3.24 to −1.95)	<0.001
SpO_2 (%)				
After induction	98.7 (1.7)	98.2 (2.4)	0.46 (0.34–0.58)	<0.001
First hour	98.6 (1.7)	97.7 (2.4)	0.86 (0.75–0.97)	<0.001
Last hour	98.8 (2.1)	98.2 (2.2)	0.65 (0.53–0.77)	<0.001
$ETco_2$ (kPa)				
After induction	4.9 (0.7)	4.9 (0.6)	0.02 (−0.01 to 0.07)	0.23
First hour	5.2 (0.7)	5.1 (0.7)	0.10 (0.06–0.13)	<0.001
Last hour	5.3 (0.7)	5.2 (0.7)	0.09 (0.05–0.13)	<0.001
Heart rate (beats min^{-1})				
After induction	75.2 (15.7)	74.3 (14.5)	0.87 (−0.16 to 1.89)	0.10
First hour	71.5 (13.8)	71.3 (14.1)	0.31 (−0.61 to 1.24)	0.51
Last hour	73.0 (13.4)	73.4 (13.5)	−0.36 (−1.30 to 0.57)	0.44
Mean arterial pressure (mm Hg)				
After induction	83.0 (18.3)	81.8 (16.8)	1.28 (0.20–2.37)	0.02
First hour	81.4 (14.4)	81.0 (14.5)	0.40 (−0.49 to 1.29)	0.38
Last hour	79.7 (13.3)	80.0 (13.4)	−0.26 (−1.07 to 0.55)	0.53
Type of anaesthesia				
Total intravenous	204/1912 (10.7)	213/1922 (11.1)	0.30 (−1.37 to 1.97)‡,§	0.72
Balanced	1708/1912 (89.3)	1709/1922 (88.9)		
Epidural analgesia	581/1911 (30.4)	560/1921 (29.2)	0.95 (−1.27 to 3.18)‡	0.40
Neuromuscular block				
Monitoring	921/1896 (48.6)	917/1907 (48.1)	0.55 (−1.47 to 2.58)‡	0.59
Residual curarisation	309/837 (36.9)	273/847 (32.2)	4.59 (1.64–7.55)‡	0.002
Total fluids (ml)	2000 (1300–3000)	2000 (1250–2866)	91.14 (9.39–172.92)	0.03
Crystalloids	2000 (1200–2500)	1800 (1075–2500)	60.53 (−9.97 to 131.05)	0.09
Synthetic colloids	0 (0–500)	0 (0–312)	19.82 (−2.84 to 42.47)	0.09
Urine output (ml)	200 (100–400)	200 (100–410)	−28.19 (−49.83 to −6.55)	0.01
Transfusion of blood products	146/1913 (7.6)	169/1924 (8.8)	−1.10 (−2.76 to 0.56)‡	0.19
Packed red blood cells	81/1433 (5.7)	107/1436 (7.5)	−1.75 (−3.45 to −0.05)‡	0.04
Fresh frozen plasma	35/1433 (2.4)	41/1436 (2.9)	−0.43 (−1.53 to 0.68)‡	0.45
Platelets	5/1433 (0.3)	12/1436 (0.8)	−0.48 (−1.04 to 0.07)‡	0.09
Blood loss (ml)	150 (50–350)	150 (50–300)	8.83 (−34.40 to 52.11)	0.69
Duration of surgery (min)	179 (128–240)	180 (127–230)	5.21 (0.17–10.24)	0.04
Duration of anaesthesia (min)	210 (160–300)	210 (160–280)	5.11 (−1.69 to 11.90)	0.14

Table 4 Primary and secondary outcomes. Data are mean (standard deviation), median (quartile 25–75) or *n* (%). All models are mixed-effect models with site as random effect and trial as a fixed effect. *P-value estimated from a fixed interaction term between treatment and trial in the model. †Effect estimate is odds ratio. 95% confidence intervals and *P*-values calculated with a mixed-effect logistic regression models with site as random effect and trial as a fixed effect. ‡Adjusted intraclass correlation coefficient and condition intraclass correlation coefficient of 0.239 and 0.238, respectively. ¶Effect estimate is mean difference. 95% confidence interval and *P*-values calculated with a mixed-effect generalised linear regression model considering an inverse Gaussian distribution with site as random effect and trial as a fixed effect. §Effect estimate is hazard ratio. 95% confidence intervals and *P*-values calculated with a (shared frailty) Cox proportional hazard model with site as random effect and trial as a fixed effect. ARDS, acute respiratory distress syndrome; IQR, inter-quartile range.

	High PEEP (*n*=1913)	Low PEEP (*n*=1924)	Unadjusted effect		
			Effect estimate (95% CI)	P-value (overall)	P-value* (trials)
Primary outcome					
Postoperative pulmonary complications	562/1905 (29.5)	620/1918 (32.3)	0.87 (0.75–1.01)†,‡	0.06	0.14
Mild respiratory failure	339/1904 (17.8)	377/1918 (19.7)	0.88 (0.74–1.04)†	0.13	0.03
Severe respiratory failure	130/1904 (6.8)	140/1918 (7.3)	0.93 (0.72–1.20)†	0.55	0.54
Acute respiratory distress syndrome	17/1905 (0.9)	22/1919 (1.1)	0.81 (0.42–1.54)†	0.51	0.61
Pulmonary infection	83/1905 (4.4)	83/1919 (4.3)	1.03 (0.74–1.43)†	0.88	0.42
Pleural effusion	174/1905 (9.1)	174/1919 (9.1)	1.05 (0.83–1.33)†	0.70	0.69
Atelectasis	190/1905 (10.0)	236/1919 (12.3)	0.79 (0.63–0.99)†	0.04	0.40
Pneumothorax	12/1905 (0.6)	11/1919 (0.6)	1.05 (0.46–2.42)†	0.91	0.08
Bronchospasm	29/1904 (1.5)	33/1918 (1.7)	0.89 (0.53–1.50)†	0.67	0.64
Secondary outcomes					
Severe postoperative pulmonary complications	396/1905 (20.8)	450/1918 (23.5)	0.85 (0.72–1.00)†	0.05	0.78
Extrapulmonary complications	284/1905 (14.9)	285/1919 (14.9)	0.99 (0.82–1.20)	0.96	0.44
Systemic inflammatory response syndrome	187/1905 (9.8)	188/1919 (9.8)	1.00 (0.80–1.25)†	0.99	0.58
Sepsis	60/1905 (3.1)	71/1919 (3.7)	0.86 (0.61–1.23)†	0.42	0.22
Septic shock	24/1905 (1.3)	29/1919 (1.5)	0.84 (0.48–1.45)†	0.53	0.75
Acute kidney injury	118/1905 (6.2)	137/1920 (7.1)	0.87 (0.66–1.13)†	0.30	0.51
Major complications	464/1905 (24.4)	516/1919 (26.9)	0.87 (0.75–1.02)†	0.10	0.90
Intraoperative adverse events					
Hypotension	784 (41.0)	579 (30.1)	1.87 (1.60–2.17)†	<0.001	0.03
Rescue for desaturation	87 (4.5)	216 (11.2)	0.34 (0.26–0.45)†	<0.001	0.03
Need for vasoactive drugs	1030/1903 (54.1)	936/1915 (48.9)	1.40 (1.19–1.65)†	<0.001	0.03
Unexpected ICU admission	167/1895 (8.8)	156/1908 (8.2)	1.15 (0.87–1.53)†	0.33	0.90
Hospital length of stay (days)	9.0 (10.8)	9.1 (11.4)	−0.00 (−0.03 to 0.03)¶	0.96	0.006
Median (IQR)	6 (3–10)	6 (3–10)			
Mortality					
7-day	7/1899 (0.4)	5/1909 (0.3)	1.40 (0.45–4.44)§	0.56	0.10
In-hospital	26/1899 (1.4)	21/1908 (1.1)	1.25 (0.70–2.23)†	0.45	0.63

(29.4%) participants randomised to receive high PEEP, compared with 620/1924 (32.2%) participants randomised to receive low PEEP (odds ratio=0.87; 95% CI, 0.75–1.01]; *P*=0.06).

There was no treatment effect between studies (*P*=0.14). Among the eight components of the composite endpoint, only atelectasis occurred less often in the high PEEP group (odds ratio=0.79; 95% CI, 0.63–0.99; *P*=0.04). In additional sensitivity analyses, after adjustment for confounders, complications between high *vs* low PEEP were not different (Supplementary Tables S5, S6, and S8).

Secondary outcomes

Severe postoperative pulmonary complications, major postoperative complications, unexpected ICU admission, and hospital length of stay mortality were not different between participants receiving high *vs* low PEEP (Table 4; Supplementary Table 5). Intraoperative rescue for desaturation was less frequent with high PEEP, although this treatment was associated with more hypotension and need for vasoactive drugs occurred more frequently with high PEEP (Table 4; Supplementary Fig. S9).

Prespecified subgroup analyses

Of nine pre-specified patient characteristics evaluated in the subgroup analyses, none had significant interactions (Fig. 1). Among the seven pre-specified procedure and care-delivery characteristics subgroup analyses (Fig. 2), only a significant interaction between PEEP and type of surgery was found, with better outcomes in patients undergoing laparoscopic surgery randomised to high PEEP with recruitment manoeuvres.

Discussion

This patient-level meta-analysis of three multicentre randomised clinical trials of intraoperative ventilation in patients undergoing general anaesthesia for surgery provides a more in-depth analysis with greater power compared with the individual studies and earlier conventional meta-analysis of studies of high PEEP *vs* low PEEP. During protective tidal volume ventilation, compared with intraoperative low PEEP, high PEEP with recruitment manoeuvres did not significantly reduce postoperative pulmonary complications. Intraoperative rescue for desaturation occurred more frequently in

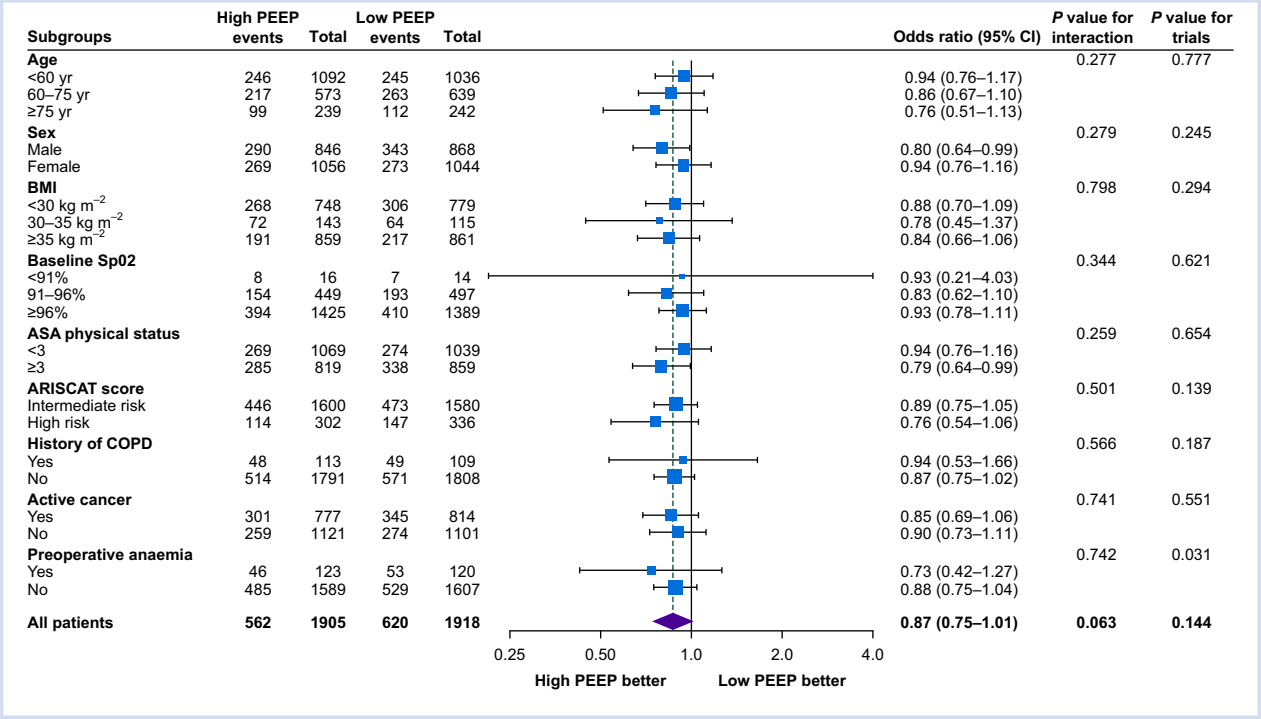


Fig 1. Postoperative pulmonary complications according to patient characteristics subgroups. Unadjusted odds ratio calculated from a mixed-effect logistic regression with trial treated as a fixed effect and site treated as a random effect. *P* values for the trial were calculated from a three-way fixed interaction between trial, treatment, and subgroup. The size of the square corresponds to the number of patients in each subgroup. ARISCAT, Assess Respiratory Risk in Surgical Patients in Catalonia; CI, confidence interval; COPD, chronic obstructive pulmonary disease.

patients in the low PEEP group, and hypotension and need for vasoactive drugs was more common in patients in the high PEEP group. These findings were consistent with the results of the original studies[9–11] and conventional meta-analyses[6,13–15].There was no evidence for any trial-specific effect.

Mechanical ventilation and general anaesthesia with muscle paralysis cause changes in lung morphology and reductions in lung volume and atelectasis that may impact adversely on intraoperative pulmonary mechanics and gas exchange.[16,17] Atelectasis and airway closure during surgery may lead to lung injury, increasing the risk of postoperative pulmonary complications.[18] The use of intraoperative high PEEP with recruitment manoeuvres prevents development of atelectasis,[19] homogenises ventilation,[20] minimises the risk of atelectrauma,[21] and decreases the driving pressure.[22] However, despite the appealing physiological rationale, no study to date was able to demonstrate improved patient-centred postoperative outcomes.

Concerns about the three original studies included the possibility that they included a low proportion of patients at 'sufficient' risk for postoperative pulmonary complications who may be expected to benefit most from preventive use of high PEEP.[23–25] The current analysis did not confirm the idea that these patients benefit more from preventive high PEEP with recruitment manoeuvres. We did find an interaction between high PEEP/recruitment manoeuvres and type of surgery, suggesting benefit in patients undergoing laparoscopic surgery. However, given the large number of subgroups analyses performed, this finding needs to be interpreted with caution and confirmed in future studies. With 16 subgroup analyses, it is expected that one analysis could be significant by chance alone. However, as a considerable number of patients are submitted to laparoscopic procedures, the possibility of a beneficial effect of high PEEP in this group should be investigated further.

In the three original studies, the event rate of severe pulmonary complications was mainly accounted for by the need for supplementary oxygen after surgery (SpO_2 <92% in room air).[23–25] In our analysis, the absolute number of severe postoperative pulmonary complications was similar between high *vs* low PEEP. Our findings regarding intraoperative events were also consistent with previous reports.[1,2,9–11,20] Intraoperative high PEEP with recruitment manoeuvres prevented desaturation but at the expense of a higher risk for hypotension. Further studies are necessary to determine the most acceptable trade-offs between PEEP and haemodynamic compromise.

Lower driving pressure may be lung protective and lead to better outcomes.[26–28] In our analysis, lower driving pressure was evident after high PEEP, compared with low PEEP. Nevertheless, this reduction was not associated with better postoperative outcome, despite the expectations raised by the results of previous observational studies.[26–29] It is important to emphasise, though, that among the original trials from which the current study used the individual patient data,[9–11] only one was designed to test a strategy aiming at maximising respiratory compliance.[10] Therefore, it cannot be ruled out that an individual titration of PEEP according to the lowest

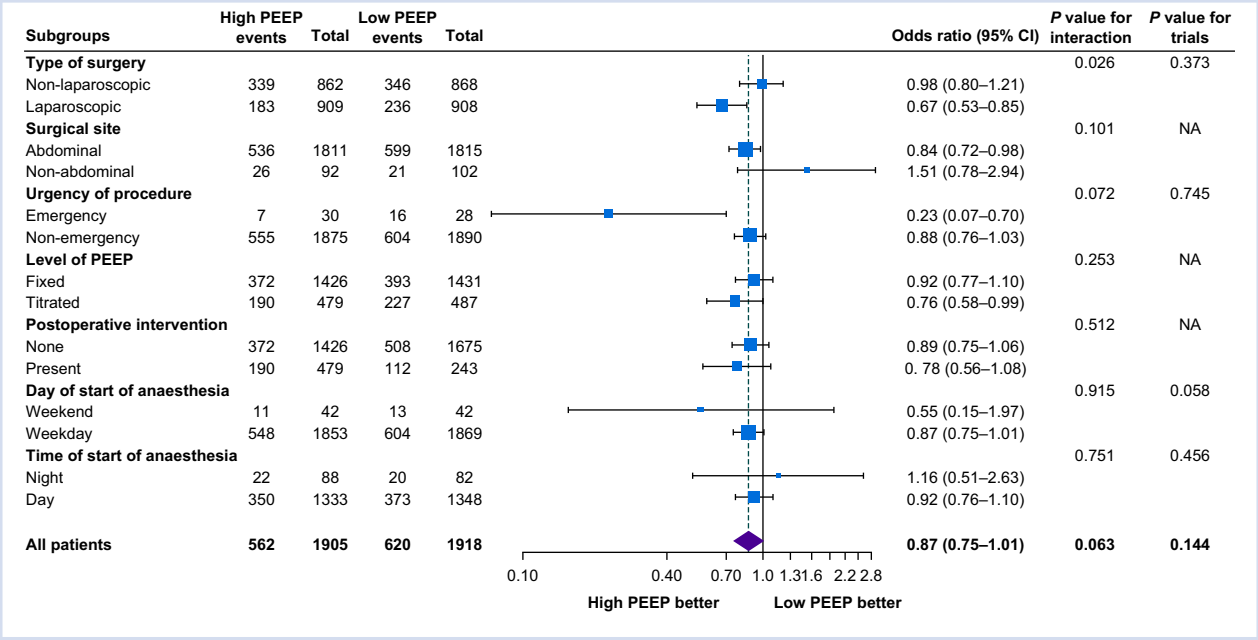


Fig 2. Postoperative pulmonary complications according to procedure and care-delivery subgroups. Unadjusted odds ratio calculated from a mixed-effect logistic regression with trial treated as a fixed effect and site treated as a random effect. *P* values for the trial were calculated from a three-way fixed interaction between trial, treatment, and subgroup. The size of the square corresponds to the number of patients in each subgroup. NA, not computed because one of the subgroups is available only in one of the trials; CI, confidence interval.

driving pressure would not lead to different results. In fact, a multicentre trial addressing the question whether individual titration of PEEP according to the driving pressure, as compared with a fixed low PEEP level, reduces postoperative pulmonary complications in patients undergoing open abdominal surgery is being conducted.[30]

In contrast to earlier observational studies[28,31] and small RCTs,[29,32] our study relies exclusively on random assignment, avoiding biases related to confounding by indication. Also, most RCTs so far focused on physiological endpoints, and not on clinically meaningful outcomes.[29,32] Nevertheless, there remain unresolved questions regarding moderate levels of PEEP (e.g. 6–8 cm H_2O), individualised PEEP titration, prolonged surgery, and laparoscopic procedures. Indeed, in two of the studies considered,[9,11] the PEEP used in the high PEEP group may have been too high, inducing overdistension rather than avoiding atelectasis.

This patient-level meta-analysis has important limitations. First, as in any meta-analysis, the results are built upon underlying internal and external validity of the three original studies. Second, although the overall sample size is large, some clinically important subgroups remained small, limiting the statistical power. Third, as the diagnosis of the components of postoperative pulmonary complications is based on clinical criteria, misclassification of patients might underestimate the observed effect; however, this factor should have equally affected the different groups analysed. Fourth, the capture of postoperative pulmonary complications after day 5 was possible but not mandatory in two of the trials,[9,11] and this could have led to underestimation of the true incidence of postoperative complications. However, the vast majority of postoperative pulmonary complications develop up to the third postoperative day,[1,10,18] and also here this factor should have equally affected both groups. Fifth, none of the trials were blinded for the intraoperative assessor, which may introduce bias. Sixth, PEEP level used in the control groups of the three original studies may not be representative of usual care in all settings. Seventh, the inclusion and exclusion criteria, the recruitment manoeuvre, and the PEEP selection was not homogeneous among the three original studies. Eight, the end of anaesthesia, and the transition from anaesthesia to awake is crucial in these patients, and this was not standardised across the trials included. Finally, the definitions of the components of the PPC were not completely standard across the included studies. However, no heterogeneity of treatment effect across trials was found.

In summary, in adults receiving general anaesthesia for non-neurological and non-cardiothoracic surgery, the combination of higher PEEP with recruitment manoeuvres (compared with low PEEP without recruitment manoeuvres) did not reduce postoperative pulmonary complications.

Authors' contributions

Full access to all of study data and responsibility for the integrity of the data and accuracy of the data analysis: NSC, ASN
Concept and design: all authors
Statistical analyses: NSC, ASN
Administrative, technical, or material support: NSC, PP, MGA, MJS, ASN
Supervision: CF, PP, MGA, MJS, ANS
The writing group vouches for the accuracy and completeness of the data and for the fidelity of the study to the protocol

All authors were involved in acquisition, analyses or interpretation of data; drafting of the manuscript; critical revision of the manuscript for important intellectual content

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Declarations of interest

TB reported receiving personal fees from Comen Eletronics Technology Co. Ltd outside of the submitted work. MGA reported receiving grants and personal fees from Drägerwerk AG and GlaxoSmithKline and receiving personal fees from GE Healthcare outside of the submitted work. ASN reported receiving personal fees from Dräger outside of the submitted work. No other disclosures were reported.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bja.2022.02.039.

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