JUSTUS-LIEBIG-UNIVERSITÄT GIESSEN

Fachbereich Medizin

Klinik und Poliklinik für Neurologie

Hirnschädigung nach herzchirurgischen Eingriffen
- Pathophysiologie, Klinik, Therapie -

Habilitationsschrift
zur Erlangung der Lehrbefähigung für das Fach Neurologie
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vorgelegt von

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Die folgende kumulative Habilitationsschrift setzt sich mit pathophysiologischen Konzepten, klinischen Erscheinungsbildern und therapeutischen Ansätzen der Hirnschädigung nach herzchirurgischen Eingriffen auseinander. Ihr liegen 8 Originalarbeiten zugrunde, die sich im Einzelnen befasst haben mit

- der Reliabilität der computergestützen Planimetrie in der experimentellen Schlaganfallforschung (A1).
  Braun T, Pukropski J, Yeniguen M, El-Shazly J, Schoenburg M, Gerriets T, Kaps M, Tschernatsch M, *Juenemann M*. Inter- and intra-rater reliability of computer-assisted planimetry in experimental stroke research. J Neurosci Methods. 2019 Jan 15;312:12-15.

- dem Einfluss der Embolusgröße in einem Rattenmodell cerebraler Luftembolisation (A2).
  Juenemann M, Yeniguen M, Schleicher N, Blumenstein J, Nedelmann M, Tschernatsch M, Bachmann G, Kaps M, Urbanek P, Schoenburg M, Gerriets T. Impact of bubble size in a rat model of cerebral air microembolization. J Cardiothorac Surg. 2013 Oct 18;8:198.

- visuellen Halluzinationen als ein häufig zu beobachtendes Phänomen nach herzchirurgischen Eingriffen (A3).
  Kastaun S, Lie SR, Yeniguen M, Schoenburg M, Gerriets T, *Juenemann M*. Pseudohallucinations After Cardiac Surgery. J Cardiothorac Vasc Anesth. 2016 Apr;30(2):466-9.

- der Durchführbarkeit einer kontinuierlichen elektroenzephalographischen Ableitung auf der Intensivstation (A4).
  Schramm P, Luczak J, Engelhard K, El Shazly J, *Juenemann M*, Tschernatsch M. Continuous electroencephalography in a mixed non-neurological intensive care population, an observational study. J Crit Care. 2017 Jun;39:62-65.

- der Prävalenz epilepsietypischer Potenziale in der kontinuierlichen Elektroenzephalographie nach offenen Herzoperationen (A5).
  Tschernatsch M*, *Juenemann M**, Alhaidar F, El Shazly J, Butz M, Meyer M, Gerriets T, Schönburg M, Schramm P. Epileptic seizure discharges in patients after open chamber cardiac surgery-a prospective prevalence pilot study using continuous electroencephalography. Intensive Care Med. 2020 Jul;46(7):1418-1424.

- der Prävalenz postoperativer kognitiver Defizite nach herzchirurgischen Interventionen und deren Alltagsrelevanz (A6).
  Kastaun S, Gerriets T, Schwarz NP, Yeniguen M, Schoenburg M, Tanislav C, *Juenemann M*. The Relevance of Postoperative Cognitive Decline in Daily Living: Results of a 1-Year Follow-up. J Cardiothorac Vasc Anesth. 2016 Apr;30(2):297-303.

- einem möglichen Behandlungsansatz postoperativer kognitiver Defizite nach Herzoperationen durch kognitives Training (A7).
  Butz M, El Shazly J, Sammer G, Tschernatsch M, Kastaun S, Yenigün M, Braun T, Kaps M, Böning A, Puvogel U, Bachmann G, Mengden T, Schönburg M, Gerriets T, *Juenemann M*. Decreasing postoperative cognitive deficits after heart surgery: protocol for a randomized controlled trial on cognitive training. Trials. 2019 Dec 16;20(1):733.

- den neuroprotektiven Eigenschaften von Erythropoietin in einem Schlaganfallmodell der Ratte (A8).
  Juenemann M, Braun T, Schleicher N, Yeniguen M, Schramm P, Gerriets T, Ritschel N, Bachmann G, Obert M, Schoenburg M, Kaps M, Tschernatsch M. Neuroprotective mechanisms of erythropoietin in a rat stroke model. Transl Neurosci. 2020 May 18;11(1):48-59.

Die nachfolgende Darstellung skizziert die Hintergründe und Zielsetzungen dieser Arbeiten (Kapitel 1, Einleitung), diskutiert ihre wesentlichen Ergebnisse (Kapitel 2, Diskussion) und gibt einen Ausblick auf zukünftige Forschungsfragen (Kapitel 3, Zusammenfassung und Ausblick). Kapitel 4 enthält die jeweiligen Originalpublikationen.

1. Einleitung

Herz-Kreislauferkrankungen stellen in der westlichen Welt immer noch die häufigste Todesursache dar. Allerdings ist in den vergangenen Jahrzehnten ein kontinuierlicher Rückgang der Sterberaten für Erkrankungen dieser Entität zu verzeichnen[1]. Diese positive Entwicklung wird vor allem Fortschritten im Bereich der Prävention und Behandlung zugeschrieben. Einerseits stellen Verhaltensänderungen sowie medikamentöse Therapien im Rahmen der Primär- und Sekundärprävention effektive Maßnahmen zur Reduktion potentieller Risikofaktoren, wie etwa der arteriellen Hypertonie, des Diabetes mellitus, Fettstoffwechselstörungen, Adipositas, Bewegungsarmut und des Rauchens dar[2]. Andererseits besitzen interventionelle, revaskularisierende Verfahren sowohl im Bereich der Herz- als auch der Hirngefäße einen immer größeren Stellenwert[3,4].

Die Zunahme invasiver therapeutischer Optionen und eine Verlängerung der Lebenserwartung rückten in den vergangenen Jahrzehnten ebenso die Qualität des Überlebens in den Mittelpunkt des wissenschaftlichen Interesses. In diesem Kontext wurden vermehrt interventions-assoziierte Hirnschädigungen wie cerebrale Ischämien, das Delir oder postoperative kognitive Defizite untersucht, die zu persistierenden Symptomen und der damit verbundenen Einschränkungen der Lebensqualität führen können[5-7].

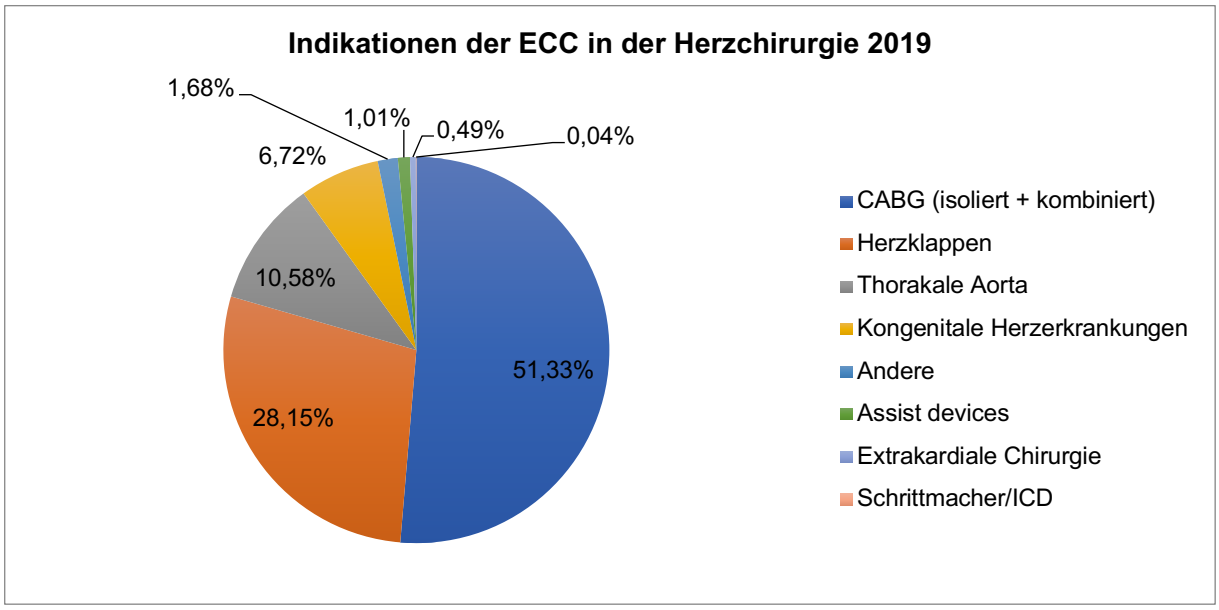
Im Vergleich zu anderen chirurgischen Disziplinen werden vor allem herzchirurgische Eingriffe mit dem Auftreten intraoperativ erlittener Hirnschädigungen in Verbindung gebracht. Insbesondere der Einsatz der Herz-Lungen-Maschine (HLM), in den 1950er Jahren von Gibbon in die klinische Praxis eingeführt, wurde diesbezüglich in den vergangenen Jahrzehnten als größter Risikofaktor gesehen[8]. Die Frage nach dem direkten Zusammenhang zwischen der HLM und dem Auftreten operations-assoziierter Hirnschädigungen wurde in Vergangenheit kontrovers diskutiert und kann bisher nicht zweifelsohne belegt werden[9].

1.1. Herzchirurgische Eingriffe in Deutschland

Die Deutsche Gesellschaft für Thorax-, Herz- und Gefäßchirurgie berichtet jährlich aus ihrem Register[10]. Diesem Bericht ist unter anderem die jährliche Anzahl in Deutschland durchgeführter Herzoperationen unter Einsatz der extrakorporalen Zirkulation (extracorporeal circulation, ECC) zu entnehmen. Obwohl in den vergangenen 10 Jahren ein Rückgang ECC-assistierter Operationen von ca. 85.000 auf 72.000 zu verzeichnen ist, bedeutet dies trotzdem für 2019 bei 78 deutschen Zentren eine Anzahl von 920 Eingriffen unter ECC pro Jahr und Zentrum[10]. Die Abnahme der entsprechenden Operationszahlen scheint vor allem der immer häufigeren Durchführung alternativer Verfahren wie beispielsweise der off-Pump Bypass-Chirurgie oder auch minimal-invasiver, endovaskulärer Interventionen an den Klappen geschuldet.

Ein Blick auf die Indikationen des HLM-Einsatzes (siehe Abbildung 1) zeigt, dass ca. 80% (79,5%) der Eingriffe Bypass- (CABG) und Herzklappenoperationen darstellen - Operationen die vor allem bei älteren Patienten durchgeführt werden. So erfolgten im Jahre 2019 33,5% der Eingriffe am Herzen an Patienten mit einem Alter von 70 – 79 Jahren, 18,6% sogar an über 80 Jährigen[10].

Abbildung 1



Modifiziert nach Beckmann et al.[10]

1.2. Der Risikopatient in einer vulnerablen Lebensphase

Das Patientenalter gilt als einer der wichtigsten Risikofaktoren für das Auftreten von Hirnschädigungen im Rahmen von Herzoperationen. Man konnte zeigen, dass im Falle von Bypass-Operationen vor allem ältere Patienten ein besonders hohes Risiko besitzen, im Rahmen der Operation neurologische Komplikationen zu erleiden oder sogar im Krankenhaus zu versterben[11-16]. Daneben konnten auch weitere patientenbezogene Risikofaktoren wie die Gebrechlichkeit (Frailty), der Ausbildungsgrad, metabolische und kardiovaskuläre Grunderkrankungen, Substanzabhängigkeit, Schlafstörungen sowie auch vorbestehende kognitive Defizite und eine Depression identifiziert werden[17,18]. Diese Faktoren, die bereits präoperativ bestehen und sich kurzfristig kaum modifizieren lassen, beeinflussen die Indikationsstellung und Planung herzchirurgischer Eingriffe, vor allem in höherem Alter, zunehmend. Sie werden um intraoperative, potentiell hirnschädigende Faktoren, wie die Dauer der extrakorporalen Zirkulation, den chirurgischen Zugangsweg, die Dosierung von Anästhetika, das Temperatur-, Blutdruck- und Blutglukosemanagement sowie die Hämodilution ergänzt[17]. Diese temporale Differenzierung

des Risikoprofils ermöglicht es prinzipiell, modifizierbare Prozesse zu identifizieren und gezielt entsprechende präventive Maßnahmen zu untersuchen. Allerdings weisen Ungenauigkeiten existierender Prädiktionsmodelle andererseits auf den Bedarf eines weiteren Wissenszuwachses auf diesem sehr heterogenen Gebiet hin[19,20].

Neben einem Abfall der gesundheitsbezogenen Lebensqualität[21] können frühzeitige Berentung sowie vermehrte gesellschaftliche Abhängigkeit, Konsequenzen einer Hirnschädigung nach Herzoperationen darstellen[22]. Besonders problematisch, sowohl für die Patienten und ihre Familien als auch für das Gesundheitssystem, erscheint hierbei, dass die postoperativen Beeinträchtigungen in einem äußerst vulnerablen Lebensabschnitt auftreten, in dem kognitive Leistungseinbußen schnell zu einem Verlust der Selbständigkeit und einer damit einhergehenden Pflegebedürftigkeit führen können[23]. Die meisten Menschen definieren sich und ihr Selbstbild in großen Teilen über ihre kognitiven Fähigkeiten. Wenn in diesem Bereich alltagsrelevante Einschnitte entstehen, stellt dies für alle Betroffenen meist eine große Belastung dar.

1.3. Pathophysiologie der Hirnschädigung

Neben der bereits erwähnten zeitlichen Einteilung potentieller Ursachen einer perioperativen Hirnschädigung existieren weitere Ansätze, die die möglichen zugrundeliegenden pathophysiologischen Konzepte - insbesondere in Verbindung mit der HLM – berücksichtigen. Diese Prozesse scheinen sich zu überschneiden und sind im Hinblick auf ihre Auswirkungen keinesfalls isoliert zu sehen, sondern bedingen und verstärken sich gegenseitig.

So kann das Trauma eines operativen Eingriffs per se oder aber der Blutkontakt zu körperfremden Oberflächen im Falle der extrakorporalen Zirkulation, eine Inflammationsreaktion anstoßen, die negative Einflüsse auf das klinische Ergebnis ausübt und an einem Spektrum postoperativer Krankheitsbilder beteiligt ist, das von Stimmungsstörungen bis hin zu neurodegenerativen Erkrankungen und persistierenden kognitiven Defiziten reicht[24,25]. Weiterhin werden anästhesiologische Medikamente und intraoperative Störungen der cerebralen Perfusion mit dem Auftreten von Schlaganfällen, deliranten Symptomen aber auch persistierenden kognitiven Defiziten in Verbindung gebracht [26-28,29]. Eines der in diesem Zusammenhang in den letzten Jahrzenten sehr häufig diskutierten pathophysiologischen Konzepte ist das der cerebralen Mikroembolien.

1.3.1. **Cerebrale Mikroembolien**

Unter Einsatz der Herz-Lungen-Maschine kommt es bei nahezu jedem Patienten zu cerebralen Mikroembolien[30,31]; hierbei zielt eine historische Einteilung des embolisierenden Materials in „micro/macro“ auf die Eigenschaft, ein 200µm Gefäß zu verschließen, ab[32]. Eine weitere Einteilung berücksichtigt die Beschaffenheit, nämlich gasförmig (Luft, Sauerstoff,

Kohlendioxid, Stickstoffmonoxid), solide biologisch (atheromatös, Calcium, Fibrin, Thrombozyten-/ Erythrozytenaggregate, Chylomikronen, Fette) sowie auch solide nicht-biologisch (PVC-Fragmente, Aluminium-Fragmente, Silikone, Knochenwachs, Handschuhpuder, Baumwollfäden)[33].

Mikroemboliesignale können intraoperativ aufgrund des hiermit einhergehenden Impedanzsprunges dopplersonographisch, am besten in der A. cerebri media über das transtemporale Schallfenster, detektiert werden[30,34]. Als kritische Zeitpunkte für das Auftreten von Embolien während der Operation unter ECC gelten vor allem die Kanülierung der Aorta, die Initiierung des extrakorporalen Kreislaufs, das Setzen und Entfernen der Aortenklemme sowie der Beginn des Herzschlages[35].

1.3.2. **Cerebrale Gasembolien**

Cerebrale Gasembolien und damit verbundene Schädigungen des zentralen Nervensystems treten häufig im Zusammenhang mit HLM-assistierten chirurgischen Interventionen auf und können hierdurch zu einer erhöhten periprozeduralen Morbidität und Mortalität beitragen[5,6,35-40]. Ausgedehnte Luftembolien mit großen Mengen embolisierenden Gases stellen hierbei eher eine Seltenheit dar und resultieren in schwersten cerebralen Schädigungen mit ausgeprägten morphologisch fassbaren Veränderungen, deren Fatalität gemäß entsprechender Ergebnisse der Grundlagenforschung und klinischer Beobachtungen unbestritten zu sein scheint[41,42]. Im Gegensatz hierzu sind die Konsequenzen cerebraler Gas-Mikroembolisationen (cerebral air microembolisation; CAM) mit kleineren Luftvolumina gegenwärtig weniger erforscht.

Die dreidimensionale Struktur der Gasbläschen innerhalb eines Gefäßes auf dem Weg vom Herzen in die Endstrombahn unterliegt einer gewissen Dynamik: Mit abnehmendem Gefäßdurchmesser scheinen Gasbläschen ihre sphärische Form zu verlieren und eine zylindrische Konfiguration anzunehmen. Hierbei können sie intakt bleiben, sich zu größeren Bläschen zusammenlagern oder in kleinere aufspalten und sich dann in Abhängigkeit von ihrer Größe perlschnurartig im Gefäßlumen formieren[43]. Größere Gasblasen, die im Gefäß steckenbleiben, verschließen cerebrale Arteriolen und können so zu einer Ischämie im flussabwärts befindlichen Versorgungsgebiet der entsprechenden Hirnarterie führen. Kleinere Gasembolien hingegen können zunächst innerhalb des Gefäßbaumes umverteilt werden und ein breites Spektrum fokal-neurologischer Symptome durch eine transiente Ischämie oder auch Schädigung des Endothels mit nachfolgender Inflammation provozieren[44,45]. Es existieren experimentelle Hinweise darauf, dass sogar Bläschen, die klein genug sind, Arteriolen und Kapillaren zu durchfließen, ohne diese zu verschließen, zu objektivierbaren neurologischen Defiziten führen können[46-48].

Erkenntnisse über das pathophysiologische Konstrukt der cerebralen Mikroembolisation, den Einfluss der Embolisationsmenge sowie der Embolusgröße und deren Auswirkungen auf das

Gehirn konnten bis dato nur indirekt gewonnen werden und besitzen mitunter spekulativen Charakter. Dies ist unter anderem dem Fehlen tierexperimenteller und klinischer Modelle, die das Volumen und die Größe gasförmiger Embolien zuverlässige erfassen und gegebenenfalls kontrollieren können, zuzuschreiben [43]. An diesem Punkt knüpfen Vorarbeiten unserer Arbeitsgruppe an, in denen wir ein Rattenmodell cerebraler Gasembolisation entwickelten, das die Situation während der Operation unter extrakorporaler Zirkulation realistisch abbilden und kontrollieren lässt. Ein weiteres methodisches Problem tierexperimenteller Forschung auf diesem Gebiet stellt die zuverlässige Untersuchung geeigneter Endpunkte dar: Traditionsgemäß ist die Hirninfarktgröße ein häufig gewählter Zielparameter, da er im Vergleich zu funktionellen Untersuchungen an Nagetieren als robuster gilt[49,50]. Die Planimetrie als das am häufigsten genutzte Verfahren zur Bestimmung der Infarktgröße wurde bis dato allerdings nicht systematisch untersucht und - obwohl es als Grundlage vieler tierexperimenteller Studien dient - ist wenig über seine Zuverlässigkeit bekannt.

1.3.3. **Klinischer Stellenwert cerebraler Gasembolien**

Neben prominenten fokal-neurologischen Symptomen stellen ebenfalls gut verifizierbare kognitive Defizite eine klinisch oft gesehene und gefürchtete Komplikation herzchirurgischer Eingriffe dar, da beide zu anhaltenden physischen und mentalen Einschränkungen bei den oft multimorbiden Patienten führen können.

Klinische Untersuchungen konnten CAM im Rahmen HLM–assistierter Eingriffe als signifikanten Prädiktor neuropsychologischer Defizite ausmachen[51-53]. So zeigte auch eine klinische Studie unserer Arbeitsgruppe, die den Wert intraoperativer Filter im Hinblick auf die postinterventionelle neuropsychologische Funktion untersuchte, dass unterschwellige CAM zur Ausbildung postoperativ objektivierbarer neuropsychologischer Defizite beiträgt[35]. Dieser Sachverhalt wird bis dato kontrovers diskutiert; systematische Übersichtsarbeiten konnten eine kausale Beziehung zwischen CAM und dem Auftreten postoperativer kognitiver Defizite weder eindeutig bestätigen noch widerlegen[54,55].

Nicht zuletzt, da HLM-assistierte Interventionen einen der Hauptgründe für CAM darstellen, wurden in der Vergangenheit Filtersysteme mit dem Ziel einer Reduktion der Luftembolien eingeführt. Gängige Filtersysteme werden hierbei in den arteriellen Schenkel der extrakorporalen Zirkulation eingebaut und agieren als Sieb, indem sie Bläschen zurückhalten, deren Durchmesser über dem der Filterporen liegt[56,57]. Diese Filter besitzen jedoch auch eine Reihe von Nachteilen: Neben einer Erhöhung des Flusswiderstandes per se kann während des Einsatzes die fortschreitende Verlegung der Systeme mit Zelltrümmern und Fibrin zu einer weiteren Erhöhung des Widerstandes bis hin zu einer Flussblockade führen. Daneben bestehen Hinweise darauf, dass diese Filter zu einer Aktivierung der Gerinnungskaskade, des Komplementsystems und somit auch zu einer Immunantwort beitragen[58]. Es ist denkbar, dass die

gitterähnliche Ultrastruktur dieser Systeme zu einer Dispersion größerer Gasbläschen zu vielen kleinen und somit zu einer Vergrößerung der gesamten Bläschenoberfläche führt. Dies wiederum könnte die potentiell schädliche Gas-Endothel-Kontaktfläche in Endstromgebieten vergrößern.

Die Verzahnung unterschiedlicher pathophysiologischer Mechanismen wird vor allem dann klar, wenn man sich vergegenwärtigt, dass alleine die Anwesenheit von Luftblasen im Blut einerseits zu Thrombozytenaktivierung, Koagulation und Initiierung des Komplementsystems[59] und andererseits zu einer prompten Reduktion des cerebralen Blutflusses führen kann[60]. Ferner scheinen gemäß der sogenannten „Washout-Hypothese“ von Caplan und Henerici die Effekte cerebraler Mikroembolien in Situationen einer reduzierten Perfusion und somit eingeschränkten Beseitigung besonders schwerwiegend[61]. Inflammatorische Vorgänge (bis zu einem systemischen inflammatorischen Response-Syndrom) können wiederum zu einer cerebralen Hypoperfusion führen.

1.4. Klinische Bilder der Hirnschädigung

1.4.1. **Hirninfarkt**

Herzoperationen unter Zuhilfenahme der Herz-Lungen-Maschine implizieren ein deutlich erhöhtes Risiko neurologischer Komplikationen, wobei der Hirninfarkt oft als eines der verheerendsten Ereignisse gilt, da er vor allem im Falle fortbestehender neurologischer Defizite sowohl das Überleben als auch die Lebensqualität deutlich reduzieren kann[62]. Ausgehend von einem Schlaganfall als klinisch objektivierbares, persistierendes fokal-neurologisches Defizit wird in der Literatur eine bemerkenswert stabile Inzidenz von 1-5% für den Zeitraum der ersten 30 postoperativen Tage angegeben[63]. Allerdings fanden Studien mit magnetresonanztomographischer (MRT) Bildgebung bei bis zu 60% der Patienten mit Bypass- oder Herzklappenoperationen postoperativ neu aufgetretene Ischämien (meist mit embolischem Muster), die bei einem großen Teil der Patienten mit fehlenden fokal-neurologischen Defiziten als `klinisch stumm` bezeichnet wurden[64-66]. Unterschiedliche kardiochirurgische Eingriffe besitzen hierbei unterschiedliche Schlaganfallrisiken: Koronararterielle Bypass-Operationen (coronary artery bypass grafting, CABG) tragen das geringste Risiko, gefolgt von kombinierten Eingriffen von CABG und dem Aortenklappen- sowie besonders dem Mitralklappenersatz[67]. Ein höheres Alter, eine vorbestehende Leukenzephalopathie, die Atheromatose des Aortenbogens und Atherosklerose weiterer peripherer Arterien sowie kardiopulmonale Bypass-Zeiten von >2 Stunden scheinen weiterhin mit einem erhöhten Risiko für intraoperative Hirninfarkte verbunden zu sein[6,68,69].

In Bezug auf die Schlaganfallätiologie während herzchirurgischer Eingriffe werden vor allem arterielle Embolien, die mit ca. 60% die häufigste Ursache darstellen, sowie Störungen der

Hämodynamik mit Ausbildung sogenannter Wasserscheideninfarkte und postoperative inflammatorische Prozesse aufgeführt[70-72]. Darüber hinaus kann ein in circa 30% der Fälle postoperativ auftretendes Vorhofflimmern zu periprozeduralen, kardioembolischen Schlaganfällen führen[73,74].

Es konnte gezeigt werden, dass perioperativ erlittene Hirninfarkte die Mortalität herzchirurgischer Patienten von 4% auf 38% erhöhen[65] und häufig eine Verlängerung des Intensiv- und Stationsaufenthaltes sowie die Entlassung in eine Pflegeinstitution bedingen[75]. Vorbestehende Schlaganfälle gelten als ein unabhängiger Risikofaktor für das Erleiden eines Delirs und können, perioperativ erlitten, ursächlich für frühe symptomatische epileptische Anfälle und auch strukturelle Epilepsien sein[19]. Eine eindeutige Assoziation zwischen akuten cerebralen Ischämien in der Magnetresonanztomographie und persistierenden postoperativen Defiziten wird kontrovers diskutiert und konnte bisher nicht eindeutig belegt werden[76].

Patienten, die sich einer Herzoperation unterziehen, messen der postoperativen Lebensqualität und Schlaganfallfreiheit eine ähnlich hohe Priorität bei wie dem kurz- und langfristigen Überleben[77]. Neben der evidenzbasierten Behandlung perioperativer Schlaganfälle sollten sich Bemühungen darauf konzentrieren, präventive Strategien zur Verringerung der Inzidenz perioperativer Schlaganfälle nach herzchirurgischen Eingriffen zu entwickeln[78]. Hierzu scheint ein multiprofessioneller Ansatz, der präoperative, intraoperative und auch postoperative Strategien beinhaltet, notwendig[77]. Die präoperative Risikokonstellation wird vor allem durch die Patientenanamnese sowie die entsprechenden Vorerkrankungen bestimmt und ist häufig – vor allem im Rahmen dringender kardiochirurgischer Interventionen – nur eingeschränkt modifizierbar. Intraoperative Strategien zur Schlaganfallprävention obliegen vor allem dem Kardiochirurgen und dem Anästhesisten[59,79]. In den letzten fünf Jahrzehnten konnte bereits durch die Modifikation intraoperativer Risikosituationen eine deutliche Reduktion der perioperativen Schlaganfallraten erreicht werden[77].

Die Entwicklung medikamentöser Neuroprotektiva in der Schlaganfallforschung zeigt bereits seit vielen Jahren enorme Probleme in der Translation erfolgversprechender Ergebnisse von der Laborbank an das Patientenbett[80]. Neben der eingeschränkten Qualität und oft fehlenden Standardisierung entsprechender Grundlagenstudien ist ein Hauptgrund hierfür, dass bei dem präklinischen Schlaganfall der Zeitpunkt des Gefäßverschlusses nicht bekannt ist und so der präventive Einsatz medikamentöser Neuroprotektiva nahezu unmöglich erscheint. Im Falle intraoperativ erlittener cerebraler Ischämien ist der Zeitpunkt jedoch bekannt. Vor diesem Hintergrund untersuchte unsere Arbeitsgruppe die präventive Gabe potentiell neuroprotektiv wirkender Substanzen in einem Schlaganfallmodell der Ratte.

1.4.2. **Delir**

In Abhängigkeit des Alters sowie der Erfassungsmethode variiert die Häufigkeit eines Delirs bei herzchirurgischen Patienten zwischen 14 – 50%[17]. In dieser Population kann die Symptomatik über Tage bis Wochen hinweg andauern[72]. Das Delir führt zu einer Verlängerung des stationären Aufenthaltes, einer erhöhten Mortalität sowie einem schlechteren funktionellen Ergebnis vier Wochen nach der Operation[81-83]. Darüber hinaus scheint es mit einem postoperativen, kognitiven Abbau nach einem und auch sechs Monaten assoziiert zu sein[84].

Gemäß des „Diagnostic and Statistical Manual of mental Disorders" (DSM-5) wird ein Delir als eine akut fluktuierende Beeinträchtigung des Bewusstseins und der Aufmerksamkeit sowie eine Veränderung der Kognition (Gedächtnis, Sprache, Orientierung) definiert, die nicht mit einer bereits bestehenden neurologischen/neurokognitiven Störung im Zusammenhang steht sowie wahrscheinlich durch eine direkte physiologische Konsequenz einer medizinischen Bedingung oder Substanzintoxikation bedingt wird[85].

Mit der Entstehung eines Delirs werden multiple Mechanismen in Verbindung gebracht. So scheinen hier im Besonderen bei herzchirurgischen Patienten eine gesteigerte Inflammation, ein Transmitterungleichgewicht, metabolische Dysfunktionen, hämodynamische Instabilität und genetische Faktoren zusammenzuspielen[86]. Diese Mechanismen können weiter durch vorbestehende kognitive Defizite, die Wahl und Menge der Sedativa, intraoperative Störungen der cerebralen Perfusion, perioperative Hirninfarkte und Infektionen aggraviert werden[87].

Die Erfahrung als klinisch tätiger Neurologe zeigt, dass im Rahmen herzchirurgischer Eingriffe isoliert optische Halluzinationen auftreten können[88]. Patienten, die diese beklagen, erfüllen darüber hinaus keine weiteren Kriterien eines Delirs und zeigen sich von diesen Trugbildern zwar distanziert, jedoch auch beunruhigt. Bis dato liegen keine systematisch erhobenen Daten über die Inzidenz, mögliche Risikofaktoren, den Verlauf oder auch die Assoziation dieser Symptomatik mit einem Delir vor, was zu einer großen Unsicherheit seitens der Patienten aber auch der behandelnden und konsultierten Ärzte führen kann.

1.4.3. **Epileptische Anfälle**

Sowohl vorbestehende als auch akute strukturelle cerebrale Schädigungen erhöhen das Risiko epileptischer Anfälle. Dies trifft im besonderen Maße auf herzchirurgische Patienten zu, da bei diesen einerseits im Rahmen der kardiovaskulären Grunderkrankung häufig bereits chronische neurovaskuläre Vorschädigungen des zentralen Nervensystems bestehen[89,90]. Andererseits birgt die kardiochirurgische Intervention per se, wie zuvor beschrieben, das erhöhte Risiko einer akuten Hirnschädigung. Retrospektive Analysen berichten eine erhöhte Inzidenz postoperativer cerebraler Ischämien und deliranter Symptome sowie eine erhöhte Mortalität bei Patienten mit epileptischen Anfällen nach herzchirurgischen Interventionen[91,92].

Die Inzidenz epileptischer Anfälle nach herzchirurgischen Eingriffen wird mit etwa 0,5-1% angegeben[91,93]. Diese Anfälle können – abhängig von der Art und dem Ort der Schädigung - sowohl fokal als auch generalisiert konvulsiv aber auch non-konvulsiv (non-convulsive seizures, NCS) auftreten. Aufgrund des Fehlens offensichtlicher klinischer Korrelate, wie beispielsweise Myoklonien oder einer ausgeprägten Steigerung des Muskeltonus, sind Letztere ohne Zuhilfenahme neurophysiologischer Untersuchungsmethoden wie der Elektroenzephalographie oft schwer zu entdecken und gelten daher als unterdiagnostiziert[93,94]. Ferner stellen die aufgeführten Inzidenzdaten lediglich das Ergebnis einer Schätzung retrospektiver Daten dar. Um zuverlässige Aussagen über die Häufigkeit und somit auch den Umfang epileptischer Anfälle nach herzchirurgischen Eingriffen zu erhalten, werden folglich prospektive Untersuchungen gefordert, die neben der klinischen Evaluation ebenfalls ein elektroenzephalographisches Monitoring beinhalten[93].

Differentialdiagnosen postoperativer Anfälle reichen von nicht-epileptischen Myoklonien über eine akute Verschlechterung vorbestehender chronischer Tremorerkrankungen bis hin zum Muskelzittern (Shivering), wie es zum Beispiel im Rahmen rascher Änderungen der Körpertemperatur oder dem Abfluten von Sedativa kommt. Oftmals ist die sichere Differenzierung klinisch nicht möglich und gelingt auch hier nur unter Zuhilfenahme der Elektroenzephalographie[94]. Die Unterscheidung hat nicht nur akademischen Charakter, sondern besitzt einen hohen praktischen Wert, da sich die therapeutischen Konzepte nicht-epileptischer Bewegungsstörungen häufig grundlegend von denen iktaler Erkrankungen unterscheiden.

1.4.4. **Postoperative kognitive Defizite**

Nach herzchirurgischen Eingriffen weisen zwischen einem und zwei Drittel der Patienten neuropsychologische Defizite (v.a. in Gedächtnisfunktionen, Aufmerksamkeit und Exekutivfunktionen) auf[89], die noch Monate und Jahre später nachweisbar sind[62,95,96].

Entsprechende Häufigkeitsangaben dieser persistierenden postoperativen kognitiven Defizite (postoperative cognitive deficits, POCD) variieren in Abhängigkeit der Definition, der verwendeten Testinstrumente und des Zeitpunktes der Testung[97,98]. Eine weit verbreitete Definition für POCD ist die Abnahme kognitiver Leistungen um eine Standardabweichung zwischen einem präoperativen und drei Monate postoperativen Messzeitpunkt, in mindestens zwei objektiv gemessenen kognitiven Funktionen (beispielsweise verbales Gedächtnis, Aufmerksamkeit, kognitive Flexibilität, Sprache oder visuomotorische Fähigkeiten)[97]. Noch nach drei Monaten sind so kognitive Defizite bei 16% bis 23%[96], nach drei Jahren sogar bei 31%[62] der Bypass-operierten Patienten (on-pump) messbar. In einer Longitudinalstudie, die den Langzeitverlauf kognitiver Defizite in der Bypass-Chirurgie untersuchte, konnte noch nach fünf Jahren bei 42% der Patienten POCD nachgewiesen werden[95].

POCD sind mit verminderter Lebensqualität[99], erhöhter Sterblichkeit[100], erhöhten wirtschaftlichen Kosten[100] und langfristiger kognitiver Abnahme[101] assoziiert. Es konnte gezeigt werden, dass ein Zusammenhang zwischen präoperativer Angst und der postoperativen Abnahme kognitiver Funktionen besteht[102]. Als weitere präoperative Risikofaktoren für die Entstehung von POCD zählen das Alter[101], eine vorbestehende Depression[102-104] und verminderte neuropsychometrische Funktionen[103,105].

Aus Studien in denen POCD testdiagnostisch objektiviert wurden, ist bekannt, dass nach Herzklappenoperationen unter extrakorporaler Zirkulation, trotz Kontrolle für Alter und weitere Risikofaktoren, kognitive Leistungsabfälle häufiger auftreten als nach koronaren Bypass-Operationen[106,107]. Darüber hinaus liegt die Rate cerebraler Mikroembolien, einem der vermeidlichen Risikofaktoren für POCD, in der Herzklappenersatzchirurgie deutlich höher als bei Bypass-Operationen[107]. Lange Zeit wurden kognitive Defizite nach Herzoperationen in erster Linie der Herz-Lungen-Maschine zugeschrieben und prägten so den Begriff des „pump-head“[9]. Übersichtsartikel, die postoperative kognitive Zielparameter nach konventionellen Bypass-Operationen unter HLM (on-pump) mit den immer häufiger durchgeführten CABP-Operationen ohne Unterstützung der HLM (off-pump) verglichen, lassen jedoch zunehmend an einer zu einseitigen Betrachtungsweise zweifeln[9,108]. Diese Erkenntnis stützt ein multifaktorielles Modell, in dem oben genannte individuelle, patientengebundene Faktoren (Vorerkrankungen, Vormedikation, kognitive Reserve) auf operationsassoziierte Variablen wie die Folgen des chirurgischen Traumas (Dysfunktion der cerebralen Autoregulation, Stressantwort, Inflammation), der extrakorporalen Zirkulation (Cerebrale Mikroembolien, Hyperthermie) sowie des intraoperativen Managements (Hämodilution, Hyperkoagulabilität, Blutdruckschwankungen) treffen[98].

Obwohl POCD im frühen postoperativen Verlauf einer deliranten Symptomatik ähneln und sich prinzipiell mit dieser überlagern können, sind sie jedoch von einem postoperativen Delir abzugrenzen[35,96]. So sind POCD nicht durch Bewusstseinsstörungen, Desorientierung oder Halluzinationen charakterisiert, sondern manifestieren sich subtiler und betreffen vorrangig die deklarativen Gedächtnis- und Exekutivfunktionen[35,66,109]. Weiterhin besteht ein Delir transient und betrifft Patienten in der frühen postoperativen Phase. Delir und POCD haben jedoch gemeinsam, dass es sich nicht um genuin psychologische oder vorrangig affektiv überlagerte Phänomene handelt. Der Einfluss etwa von Depression oder Angst erklärt nicht, wieso es postoperativ zu einer neuropsychologischen Leistungsminderung kommen kann[109]. Einige Studien geben jedoch Hinweise darauf, dass das postoperative Auftreten eines Delirs kognitive Defizite verursachen oder zumindest begünstigen kann[96,110,111].

Neben Unsicherheiten bezüglich einer geeigneten neuropsychologischen Testbatterie sowie der damit einhergehenden Definition postoperativer kognitiver Defizite wurde in den vergangenen Jahren wiederholt diskutiert, inwieweit dieses theoretische Konstrukt wirklich praktische Relevanz besitzt. Es wurde bisher nicht untersucht, ob kognitive Defizite zu messbaren

Einschränkungen der Alltagskompetenz Betroffener führen und ob diese Symptomatik von Patienten selbst und/oder nahestehenden Angehörigen wahrgenommen wird. Damit verbunden ist ebenfalls die Frage nach der Behandlungsindikation dieser postoperativen Störungen. Über den Nutzen, die Modalität (medikamentös oder in Form eines kognitiven Trainings), Zeitpunkt und Dauer finden sich in der gegenwärtigen Literatur keine überzeugenden Daten[17].

1.5. Synopsis der Ziele eigener Untersuchungen

Vor dem Hintergrund der gegenwärtigen Bevölkerungsstruktur in den Industrienationen sowie der prognostizierten Entwicklung mit einer Zunahme des Anteils älterer, multimorbider Patienten ist ein weiterer Anstieg kardiochirurgischer Eingriffe sowie deren neurologisch/neuropsychologischer Folgeschäden zu erwarten[112,113]. Gegenstand der vorliegenden Arbeit ist die Untersuchung der zugrundeliegenden Pathophysiologie, die Diskussion unterschiedlicher klinischer Erscheinungsbilder sowie das Aufzeigen möglicher therapeutischer Konzepte und präventiver Ansätze. Hierbei werden sowohl Ergebnisse eigener tierexperimenteller als auch klinischer Studien berücksichtigt.

Im Rahmen tierexperimenteller Neuroprotektionsstudien ist die Hirninfarktgröße traditionsgemäß ein häufig gewählter Zielparameter[49]. Im Vergleich zu globaleren Größen, wie beispielsweise der Erfassung motorischer, sensorischer oder koordinativer Funktionen, erscheint die Messung eines Infarktvolumens weniger anfällig für Störfaktoren und stellt somit einen vermeintlich robusteren Endpunkt dar, um die Effizienz einer Therapie zu prüfen[50]. In einer eigenen Untersuchung wurde zunächst die intra- und inter-rater Reliabilität des zur Infarktgrößenbestimmung am häufigsten benutzten Verfahrens - der Planimetrie – an einem Rattenmodell des ischämischen Hirninfarktes untersucht, um die entsprechenden Erkenntnisse dann anschließend in den folgenden tierexperimentellen Studien nutzen zu können (A1)[114].

Wie auch unsere Arbeitsgruppe in klinischen Untersuchungen zeigen konnte, scheinen Embolien durch gasförmige Bläschen wesentlich zu Hirnschädigungen während herzchirurgischer Eingriffe unter Einsatz der Herz-Lungen-Maschine beizutragen[35]. Filtersysteme sollen das Ausmaß dieser potentiell schädlichen Embolisationen reduzieren, die netzartige Struktur dieser Filter könnte allerdings ebenfalls zu einer Dispersion größerer Bläschen in viele kleinere führen. Nicht zuletzt aufgrund bisher fehlender entsprechender Tiermodelle und der fehlenden Möglichkeit, das Volumen gasförmiger Embolien zuverlässig zu messen und zu kontrollieren, ist das Wissen um die Auswirkungen cerebraler Gasembolien und den Einfluss der Bläschengröße auf die Infarktentstehung begrenzt[43]. Unsere Arbeitsgruppe entwickelte ein Rattenmodell zur Untersuchung cerebraler Gasembolien, das die Situation während Operationen unter extrakorporaler Zirkulation simuliert[115]. Ziel war es, Machbarkeit und Zuverlässigkeit der Produktion sowie Embolisation von Gasbläschen mit unterschiedlichen, definierten Durchmessern zu untersuchen. Darüber hinaus wurden Embolisationseffekte im Hinblick auf das funktionell-neurologische Ergebnis, die Häufigkeit und das Volumen der cerebralen Ischämie in Abhängigkeit vom Blasendurchmesser erfasst (A2)[115].

Die Vielfalt perioperativer Hirnschädigung wurde bereits einleitend erwähnt. Viele Patienten werden nach größeren Herzoperationen einem Konsiliarius der Neurologie vorgestellt, da sie über visuelle Halluzinationen klagen[88]. Häufig scheinen diese Halluzinationen isoliert aufzutreten und nicht Teil eines deliranten Syndroms oder einer psychiatrischen Erkrankung im

engeren Sinne zu sein. Im Folgenden werden drei Fälle von Patienten mit diesen Beschwerden genauer analysiert[116]. Um die Inzidenz dieses bisher nahezu unbekannten Phänomens abzuschätzen, wurden darüber hinaus 100 konsekutive Patienten 48 +/- 12 Stunden nach der Herzoperation mit einem Fragebogen untersucht, der auf Veränderungen in ihrer visuellen Wahrnehmung einging (A3)[116].

Retrospektive Untersuchungen berichten, dass Patienten mit konvulsiven oder nicht-konvulsiven epileptischen Anfällen nach Herzoperationen eine erhöhte Inzidenz von Schlaganfällen und einem Delir sowie eine erhöhte Mortalität aufweisen[91,92]. Diese Studien berücksichtigten entweder klinisch eindeutige, generalisierte Anfälle und übersahen so nicht-konvulsive Anfälle oder stellten die Diagnose durch eine entsprechende elektroenzephalographische (EEG) Ableitung, deren Indikationsstellung jedoch unklar blieb oder deren Elektrodenplazierung unterhalb des Haaransatzes wahrscheinlich zu einer Unterschätzung der tatsächlichen Inzidenz führte. Wir prüften die Machbarkeit einer kontinuierlichen EEG-Ableitung über mind. 24h und einer 10- Kanal-Registrierung im Bereich des gesamten behaarten Kopfes (A4)[117]. Diese Methodik diente dann in einer Pilotstudie dazu, die Inzidenz epileptischer Anfälle nach Herzoperation unter extrakorporaler Zirkulation zu bestimmen (A5)[118].

Postoperative kognitive Defizite sind eine weitere häufige Folge herzchirurgischer Eingriffe[7]. Bislang blieb unklar, inwieweit dieses in der Regel durch psychometrische Testergebnisse definierte Konstrukt wirklich Alltagsrelevanz besitzt und wie lange diese Defizite für den Patienten selbst oder Angehörige spürbar sind. Ziel der hier präsentierten COFAS-Studie war die quantitative und qualitative Erfassung postoperativer kognitiver Defizite mithilfe einer strukturierten Selbst- und Fremdbeurteilung durch nahestehende Angehörige im Verlaufe des ersten postoperativen Jahres (A6)[119].

Basierend auf den unterschiedlichen pathophysiologischen Konzepten der Hirnschädigung während Herzoperationen wurde im Laufe der vergangenen Jahrzehnte eine Evidenz für Präventionsstrategien geschaffen, die vor allem intraoperativ in der Verantwortlichkeit des operierenden Chirurgen oder Anästhesisten liegen[59,79]. Prospektive, systematische Untersuchungen, die den gesamten Effekt dieser Maßnahmen analysieren, fehlen jedoch[120]. So ist es vor diesem Hintergrund zwar möglich, das Auftreten von Folgeschäden zu reduzieren, man kann jedoch davon ausgehen, dass fast die Hälfte aller Patienten weiterhin kognitive Defizite beklagt[59]. Über postoperative Behandlungsmöglichkeiten kognitiver Defizite liegen gegenwärtig keine überzeugenden Daten vor. In der durch die Kerckhoff-Stiftung Bad Nauheim und die Deutsche Stiftung für Herzforschung geförderten INCOGNITO-Studie möchten wir erstmalig untersuchen, inwieweit ein kognitives Trainingsprogramm in den ersten drei Wochen der Rehabilitation einen Beitrag zur Reduktion postoperativer kognitiver Defizite leisten und damit verbunden eine Verbesserung der Lebensqualität und möglicherweise auch den Erhalt der Selbständigkeit im Anschluss an die medizinische Rehabilitation fördern kann[121]. Zur

Überprüfung dieser Fragestellung entwickelten wir ein entsprechendes Studiendesign, dessen zentrale Intervention ein alltagsnahes, auf die Fähigkeiten dieses Patientenkollektivs ausgerichtetes, kognitives Trainingsprogramm darstellt (A7)[121].

Positive Ergebnisse pharmakologischer Neuroprotektionsstudien in der Grundlagenforschung ließen sich bisher nicht in größeren klinischen Studien reproduzieren[80]. Präventive pharmakologische Maßnahmen können in der klinischen Situation, in der ein Gefäßverschluss bereits vorliegt, nur schwer ergriffen werden. Im Falle intraoperativ erlittener Hirninfarkte ist hingegen der Zeitraum der Schädigung bekannt; dies ermöglicht prinzipiell die präventive Gabe potentiell neuroprotektiver Substanzen. Wir untersuchten die neuroprotektiven Eigenschaften einer präventiven Erythropoietin-Gabe an einem Rattenmodell des Schlaganfalls im Hinblick auf Schlaganfallgröße, cerebrale Perfusion und Ödementstehung[122]. Hierbei erfolgte nach der Applikation von Erythropoietin und anschließender Ischämieinduktion eine multimodale Erfassung der Zielparameter durch die Magnetresonanztomographie, Flachdetektor-Computertomographie sowie histologische Techniken (A8)[122].

2. Diskussion

2.1. Tierexperimentelle Studien zur Ätiologie der Hirnschädigung während herzchirurgischer Eingriffe

2.1.1. Die Planimetrie in der experimentellen Schlaganfallforschung

Die Hirninfarktgröße ist in der tierexperimentellen Neuroprotektionsforschung ein häufig gewählter Endpunkt, um die Effizienz unterschiedlicher Therapien zu vergleichen. Ihre exakte Bestimmung stellt somit die unverzichtbare Basis entsprechender Studiendesigns, wie auch der in dieser Arbeit aufgeführten und diskutierten Untersuchungen, dar[115,122]. Der Einsatz computergestützter Verfahren zur Infarktgrößenbestimmung lässt zwar ein gewisses Maß an Objektivität vermuten, dennoch muss während des Prozesses der Datenerfassung von einer Prüferabhängigkeit ausgegangen werden.

Wir untersuchten, ob und inwieweit in der computergestützten Planimetrie von Läsions- (LV) und Hemisphärenvolumina (HV) untersucherabhängige Variationen existieren (A1)[114]. Nagel und Mitarbeiter zeigten zuvor eine gute inter-rater Reliabilität der Planimetrie bei MR-Bildern, die abhängig von dem zeitlichen Abstand zwischen Gefäßverschluss und MRT-Untersuchung war [123]. Eine weitere Studie beschrieb eine geringere Reliabilität der konventionellen Planimetrie verglichen mit einer ergänzenden Software-Unterstützung (durch ein ImageJ Makro) an Triphenyltetrazoliumchlorid gefärbten Gehirnschnitten[49]. Beide Studien berücksichtigten und kontrollierten nicht die Untersuchererfahrung, die – wie Bratane und Mitarbeiter zeigen konnten - einen deutlichen Einfluss auf die Zuverlässigkeit und Vergleichbarkeit der Planimetrieergebnisse hat[124]. Letzteres unterstützen unsere Daten, so konnten wir eine Zunahme der inter-rater Reliabilität in den ersten sieben Wochen beobachten[114]. Über den darauffolgenden Zeitraum von 15 Monaten blieb diese auf vergleichbar hohen Werten (Krippendorffs Alpha>0,88), ferner zeigte der Bland-Altman-Plot in Abwesenheit systematischer Fehler eine solide Übereinstimmung zwischen den Bewertern[114]. Die Übereinstimmung eines Bewerters im zeitlichen Verlauf (intra-rater) war jedoch schwächer als die zwischen den Auswertern (inter-rater); dies zeigt, dass selbst ein erfahrener Untersucher Daten mit deutlichen Variationen generieren kann, was im Studiendesign und bei der Interpretation der planimetrischen Daten berücksichtigt werden sollte[114].

Problematisch bei Validitätsuntersuchungen der Planimetrie erscheint, dass kein Goldstandart zur Quantifizierung des exakten Läsions- und Hemisphärenvolumens existiert. Grundsätzlich kann das Volumen einer Gehirnhemisphäre gemäß dem Archimedischen Prinzip durch die Verdrängung von Wasser bestimmt werden. Allerdings lässt sich dies auf ein irregulär

geformtes Schlaganfallvolumen nur schwer übertragen. Ein weiterer Ansatz für die Volumetrie ist die euklidische Geometrie. Hier wird das Läsionsvolumen näherungsweise mit einfachen geometrischen Modellen (Kugel, Ellipsoid, Zylinder) berechnet. Diese Modelle neigen dazu, die wahren Ausmaße der Läsion zu über- oder zu unterschätzen. Das sphärische Modell scheint im Vergleich zur Planimetrie hier die besten Ergebnisse zu erzielen[125]. Wie bereits erwähnt, sind ischämische Läsionen jedoch in der Regel unregelmäßig geformt, so dass diese Modelle zu einer Vereinfachung und daher Ungenauigkeit tendieren. Obwohl es akzeptabel erscheint, ein sphärisches Modell für entsprechend geformte ischämische Läsionen zu verwenden, unterscheidet sich die Form der ischämischen Läsion in der Regel zu sehr von geometrischen Modellen. Für den Schlaganfall im Menschen wurde dies bereits nachgewiesen[126]. Darüber hinaus existieren unterschiedliche automatisierte Methoden zur Volumetrie: Durch die Definition einer ischämischen Schwelle des Diffusionskoeffizienten („apparent diffusion coefficient“, ADC) kann ein automatisiertes Programm das ischämische Volumen anhand dieser Werte auf dem entsprechenden MRT-Bildmaterial definieren[127]. Alternative Ansätze bedienen sich der unterschiedlichen Grauwerte in MRT-Bildern[123]. Beide Methoden sind schnell, automatisiert und benutzerunabhängig. Sie können jedoch für die Messung des gesamten Hemisphärenvolumens nicht verwendet werden.

Unsere Daten deuten darauf hin, dass die computergestützte Planimetrie eine geeignete Methode zur Bestimmung des Hemisphärenvolumens oder des ischämischen Läsionsvolumens bei Nagetieren sein kann, ihre zuverlässige Anwendung allerdings eine ausreichend lange Lernphase benötigt[114]. Eine Einarbeitungszeit von circa zwei Monaten sollte in das Versuchsdesign einbezogen werden. Dies wurde im Folgenden bei entsprechenden eigenen Untersuchungen berücksichtigt[115,122].

2.1.2. **Cerebrale Gas-Mikroembolisation**

Wie auch unsere Arbeitsgruppe in klinischen Untersuchungen zeigen konnte, treten gasförmige Mikroembolien regelmäßig während herzchirurgischer Eingriffe unter Einsatz der Herz-Lungen-Maschine auf[30,31,35]. Klinisch gebräuchliche Filtersysteme können neben der angestrebten Reduktion der Blasenmenge jedoch auch zu einer Dispersion großer Gasblasen in kleinere und damit zu einer Vergrößerung der Grenzfläche zwischen Gas, Flüssigkeit und Endothel führen und so durch die Aktivierung einer inflammatorischen Antwort sowie des Komplement- und Gerinnungssystems eine weitere Gewebsschädigung forcieren[58,128-130]. Wir evaluierten Machbarkeit und Zuverlässigkeit der Produktion und Embolisation von Gasbläschen mit unterschiedlichen, definierten Durchmessern anhand eines von uns neu entwickelten Tiermodells der cerebralen Gas-Mikroembolisation (cerebral air microembolization, CAM) (A2)[115].

Bis zum heutigen Zeitpunkt nutzte die Grundlagenforschung im Hinblick auf Mikroembolisationen vor allem Lungenmodelle. Wissenschaftliche Erkenntnisse über die sehr heterogene Entität cerebraler Gasembolien sind folglich in der Literatur wenig zu finden[58]. Jahrzehnte standen technische Probleme wie die Schwierigkeit einer selektiven arteriellen Luftinjektion, die Unterbrechung des physiologischen cerebralen Blutflusses, exzessive Luftvolumina und stark schwankende Bläschengrößen einer standardisierten und reliablen Untersuchung der CAM im Wege[131]. Mit der Zeit wurden entsprechende Tiermodelle verfeinert und so konnten die meisten Probleme behoben werden. Sämtliche tierexperimentelle Studien über CAM, so auch oben erwähnte, nutzen zur Simulation der Gasembolien Injektionen verschiedener Luftvolumina als Bolus oder repetitiv und titrieren die Luftmenge bis zu einem bestimmten Maß an struktureller Hirnschädigung[43,132]. Dies beinhaltet jedoch weder die Darstellung noch die Verifizierung der Größe einzelner Luftblasen. Bezüglich des eigentlichen Stellenwertes durchaus kontrovers diskutiert war die Kontrolle der Bläschengröße in Tiermodellen für CAM bisher immer noch schwierig; so sind der Literatur auch hier kaum Angaben über die Bedeutung dieses Parameters zu entnehmen. Des Weiteren konnte man durch oben beschriebene Methodik der Bolusinjektion einen „Schauer“ von Luftbläschen, wie er mit hoher Wahrscheinlichkeit in der klinischen Realität zu finden ist, nicht sicher simulieren [133]. Die vorliegenden Untersuchungen der CAM wurden an einem neuen, durch unsere Arbeitsgruppe etablierten Rattenmodell durchgeführt, die die Applikation gasförmiger Embolien unter erhaltenem physiologischen cerebralen Blutfluss ermöglicht[134].

Bisher wiesen entsprechende Studien auf eine dosisabhängige Toxizität des Luftvolumens hin: In einer Vorstudie konnten wir schlechtere klinische Ergebnisse mit einer zunehmenden Anzahl 160 µm großer Luftembolien objektiveren[134], Jungwirth und Kollegen fanden eine dosisabhängige Beziehung zwischen CAM einerseits und dem Überleben sowie den neurologischen und histologischen Ergebnissen andererseits[135]. Die vorliegende Arbeit untersucht die Produktion und Embolisation verschiedener Embolusgrößen mit derselben Gesamtmenge injizierter Luft von 86 nl[115]. Das verwendete Modell ist prinzipiell in der Lage, Gasblasen mit einem Durchmesser von 40 – 250 µm zu produzieren - wir entschieden uns mit 45 µm und 160 µm für Größen, die im Grenzbereich des technisch sicher Möglichen liegen. Hinsichtlich der Anzahl und des Durchmessers der Gasblasen konnten wir sowohl die Machbarkeit als auch Zuverlässigkeit der Produktion und Injektion dieser Gasbläschen mit einer geringen Standardabweichung nachweisen[115]. Die Embolisation führte für beide Größen regelmäßig zu ischämischen Hirninfarkten sowie konsekutiv zu einer signifikanten funktionell-neurologischen Verschlechterung der entsprechenden Versuchstiere[115].

Eine Abnahme der Bläschengröße von 160µm auf 45 µm bei konstantem Injektionsvolumen bedeutete eine Zunahme der gesamten Oberfläche um das Vierfache. Trotz dieser Oberflächenvergrößerung gelang es uns nicht, signifikante Unterschiede zwischen den beiden

Gruppen bezüglich des funktionalen Ergebnisses, der Anzahl an Hirninfarkten oder deren Größe zu detektieren. Lediglich eine Tendenz hin zu größeren Infarkten bei kleineren Gasbläschen war zu verzeichnen[115]. Neben statistischen Ursachen sind hier pathophysiologische Überlegungen aufzuführen: Wenn auch nicht bewiesen, erscheint es einleuchtend, dass Gasblasen unterschiedlichen Durchmessers auch in Gefäßen unterschiedlicher Größe stecken bleiben[43]. Auf ihrem Weg durch die gehirnversorgenden Arterien können sie dennoch innerhalb kürzester Zeit ihre Größe verändern, sich aufteilen oder aneinanderlagern. Dies könnte zu einer fast einheitlichen Gasbläschengröße im Bereich der Mikrovaskulatur und somit zu einer vergleichbaren Anzahl und Größe der Hirninfarkte sowie Ausprägung der klinischen Defizite im Rattenmodell führen. Darüber hinaus gibt es experimentelle Hinweise darauf, dass selbst Gasblasen, die klein genug sind, um Arteriolen und Kapillaren zu durchfließen ohne das Gefäß nachweislich zu verschließen, zu neurologischen Defiziten führen können[46,48,60]. Die Diskrepanz zwischen funktionell-neurologischer Verschlechterung und Infarktvolumen in den Interventionsgruppen, ergänzt durch die Beobachtung, dass je eine Ratte in jeder Interventionsgruppe eine klinische Verschlechterung ohne korrespondierende Ischämie in der MRT zeigte, stellt den Hirninfarkt als einziges pathologisches Korrelat einer CAM-vermittelten Gewebeverletzung in Frage[115]. Klinische Studien haben gezeigt, dass nicht jeder Patient mit kognitiver Verschlechterung nach einer HLM-unterstützten chirurgischen Intervention MRT-detektierbare morphologische Veränderungen wie z.B. einen ischämischen Schlaganfall erleidet[35]. Dies lässt annehmen, dass ein wesentlicher Anteil der cerebralen Schädigungen, die nach der Intervention symptomatisch werden, immer noch jenseits der Nachweisgrenze der MRT liegt[35,90,136-138]. Kleinere klinische Beobachtungsstudien konnten darüber hinaus einen direkten Zusammenhang zwischen gasförmigen Mikroembolisationen und einer Hirnschädigung bisher noch nicht herstellen[30,31].

Nicht zuletzt aufgrund der Vielzahl unterschiedlicher existierender Tiermodelle sind Determinanten und Grenzwerte für morphologische oder kognitive Schädigungen durch subtile CAM sowie pathophysiologische Veränderungen mit "substruktureller" Schädigung noch undefiniert und bedürfen weiterer experimenteller Daten[58,135]. Unser Tiermodell der CAM bietet ein stark kontrolliertes Setting, das helfen kann, Schwellenwerte für eine neurologische Verschlechterung ohne offensichtliche morphologische Änderungen zu definieren[115].

2.2. Klinische Korrelate der Hirnschädigung

2.2.1. **Visuelle Halluzinationen nach Herzoperationen**

Bekanntermaßen zählen zu den neurologischen Komplikationen kardiochirurgischer Eingriffe ischämische und hämorrhagische Schlaganfälle, das postoperative Delir, die postoperative

Abnahme kognitiver Funktionen, epileptische Anfälle, cerebrale Hyperperfusionssyndrome, Hirnnervenläsionen sowie periphere Neuropathien[5,72]. In der Regel ist die entsprechende Symptomatik den behandelnden Chirurgen bekannt und es werden weitere diagnostische und - wenn verfügbar - therapeutische Schritte eingeleitet[72]. Im Rahmen neurologischer Konsiluntersuchungen werden jedoch immer wieder Patienten vorgestellt, die über wiederkehrende Sehstörungen im Sinne optischer Halluzinationen klagen. Informationen über Auftreten und Ätiologie dieses Phänomens bei Patienten nach Herzoperationen sind kaum verfügbar. Mit dem Ziel einer ersten strukturierten Erfassung wurden in einer Fallserie drei exemplarische Patienten mit diesen Beschwerden genauer analysiert (A3)[116]. Zur Abschätzung der Inzidenz dieses Phänomens diente ferner eine Pilotuntersuchung, bei der 100 konsekutive, Patienten 48 +/- 12 Stunden nach CABG oder Aortenklappenersatz unter Einsatz der HLM mit einem Fragebogen auf visuelle Halluzinationen hin untersucht wurden (A3)[116].

Wir identifizierten 11/100 (nach DSM-5)[85] nicht-delirante Patienten mit Halluzinationen nach CABG oder Aortenklappenersatz, die sich der Irrealität ihrer Wahrnehmung bewusst waren; die neurologische, neuropsychologische, psychiatrische und augenärztliche Untersuchung ergab keine relevante Pathologie. 5 dieser 11 Patienten erhielten in Abwesenheit von Kontraindikationen ein MRT des Neurocraniums. Nur ein Patient zeigte mehrere kleine, embolische Hirninfarkte im Versorgungsgebiet der rechten A. cerebri posterior[116]. Eriksson et al. untersuchten die Symptome des Delirs nach einer koronaren Bypass-Operation: Bei 12 von 52 eingeschlossenen Patienten wurde ein Delirium diagnostiziert. Es wurde im Vergleich zu unserer Beobachtung eine bemerkenswert höhere Rate (50%) nicht-deliranter Patienten mit Halluzinationen nach CABG berichtet. Allerdings fehlen hier detaillierte Informationen über Konfiguration, Häufigkeit, Dauer und der Distanzierung der Patienten[88]. In einer kürzlich publizierten Beobachtungsstudie wurde das Auftreten eines Delirs sowie von Halluzinationen sämtlicher Modalitäten bei einem gemischt-herzchirurgischen Kollektiv sowie ambulant geführten kardiologischen Patienten untersucht. Chirurgische Patienten erlebten signifikant mehr Halluzinationen als Patienten der konservativen Kontrollgruppe. 21,9% der herzchirurgischen Patienten berichteten Halluzinationen während der ersten vier postoperativen Tage. Die Mehrheit der Halluzinationen war optischer Natur, 77,3% dieser Patienten entwickelten kein Delir[139].

Weitere Informationen zu diesem Phänomen lassen sich bestenfalls aus wenigen Fallberichten ableiten: Eissa et al. berichteten über einen Patienten mit visuellen Halluzinationen in den ersten drei Tagen nach einer elektiven CABG[140], Laloux et Osseman publizierten einen Fall von postoperativen Halluzinationen am zweiten Tag nach Karotisendarteriektomie und CABG[141]. Beide Patienten klagten jedoch nur über Halluzinationen bei geschlossenen Augen, und in beiden Fallberichten fehlten MRT-Daten.

Im Hinblick auf mögliche Differentialdiagnosen erscheint eine migräniforme oder epileptische Symptomatik aufgrund der diesbezüglich leeren Eigenanamnese und familiären

Vorgeschichte, der geringen Stereotypie der Symptomatik, fehlender Kopfschmerzen sowie Abwesenheit jeglicher Bewusstseinsstörung oder peri-iktaler Symptome unwahrscheinlich.
Zur Differentialdiagnose visueller Halluzinationen gehört die pedunkuläre Halluzinose (PH), die bisher einmalig im Zusammenhang mit einer kardialen Intervention beschrieben wurde[142]. Sie führt zu komplexen Halluzinationen, die den hier berichteten sehr ähnlich zu sein scheinen, aber mit strukturellen Läsionen des Mittelhirns und/oder des Thalamus assoziiert sind[143]. Die meisten Patienten mit einer PH weisen abnorme Schlafmuster mit nächtlichen Wachphasen und abnormer Tagesschläfrigkeit auf. Darüber hinaus zeigen die visuelle Symptome eine circadiane Rhythmik mit vermehrtem Auftreten in den Abendstunden sowie oft eine Beteiligung weiterer Sinnesmodalitäten (taktil, auditiv)[144]. Okulomotorische Störungen, eine beeinträchtigte Weckreaktion, Dysarthrie und Ataxie stehen häufig im Zusammenhang mit der PH[145]. Obwohl unsere Patienten eine mit der PH vergleichbare visuelle Sinnestäuschung erlebten, bot keiner ein pathologisches Schlafmuster oder ein nachweisbares fokales neurologisches Defizit; eine strukturelle Läsion des Mittelhirns oder des Thalamus ließ sich in der MRT (einschließlich diffusionsgewichteter Sequenzen) nicht darstellen.
Visuelle Halluzinationen wurden bei älteren Patienten mit einer ausgeprägten Beeinträchtigung der Sehschärfe, beispielsweise aufgrund einer Makuladegeneration, Retinopathie oder einer Hornhauterkrankung beschrieben. Dieses sogenannte Charles - Bonnet Syndrom (CBS) ist durch lebhafte, wiederkehrende visuelle Halluzinationen bei seelisch gesunden Patienten charakterisiert, die sich vollständig von diesen Erscheinungen distanzieren können. Wie bei unseren Patienten sind die Symptome auf die visuelle Modalität beschränkt[146,147]. Neben okulären Ursachen können prinzipiell jedoch Läsionen in jedem Bereich der zentralen Sehbahn ein solches "Release-Phänomen" als Folge der Deafferenzierung des visuellen Inputs im extrastriatalen visuellen Assoziationskortex begünstigen[144,148-150]. Wie die augenärztliche Untersuchung dokumentierte, hatten alle von uns untersuchten Patienten ein normales oder nur leicht altersentsprechend beeinträchtigtes Sehvermögen, keine morphologisch darstellbaren Läsionen innerhalb der Sehbahn und nur eine verhältnismäßig kurze Dauer der Symptome (2 bis 4 Wochen)[116]. Die vorliegenden Fälle scheinen daher eher eine separate Krankheitsentität darzustellen.
Es ist denkbar, dass Halluzinationen nach einer Herzoperation einer mikroembolischen Schädigung der zentralen Sehbahn entsprechen. Untersuchungen, die eine Einzelphotonenemissions-Computertomographie des gesamten Gehirns mit dem transkraniellen Doppler nach einer Bypass-Operation kombinierten, konnten eine bevorzugte Embolie-Ablagerung im okzipitalen Kortex zeigen[151], die möglicherweise unterhalb der Nachweisgrenze der konventionellen MRT liegt. Visuelle Halluzinationen stellen dann ein klinisches Korrelat der elektrophysiologischen Übererregbarkeit während des Prozesses der kortikalen Reorganisation dar[152]. Darüber hinaus zeigten Studien mit einer multiaxialen Zentrifuge vorübergehende Sehstörungen wie

optische Halluzinationen in Verbindung mit einer gestörten Sauerstoffversorgung des Hirngewebes[153,154] - ein Umstand, der während und früh nach einer Bypass-Operation beschrieben wurde[155,156].
Mehrere Fallberichte berichten von verschiedenen Arten postoperativer Halluzinationen im Zusammenhang mit Anästhetika und Analgetika, die auch den hier beobachteten Patienten verabreicht wurden[157-159]. Allerdings sind die meisten dieser Medikamente Teil der Standardtherapie bei größeren Herzoperationen, kausale Zusammenhänge lassen sich aus diesen Daten nicht ohne Weiteres ableiten. In unserer Untersuchung wurden visuelle Halluzinationen nicht mit dem postoperativen Delir in Verbindung gebracht[116]. Es sind größere, systematische Studien erforderlich, um einen Zusammenhang vollständig auszuschließen und eine mögliche Rolle vorbestehender Störungen, medikamentöser Therapien sowie demographischer Variablen bei diesem Phänomen zu klären.

Im Hinblick auf mögliche klinische, wirtschaftliche und lebensqualitätsbezogene Konsequenzen sollten die behandelnden Ärzte die Benignität transienter postoperativer visueller Halluzinationen, die nicht mit einem Delir oder offensichtlichen strukturellen Hirnschäden assoziiert sind, kommunizieren. Patienten könnten unnötigerweise mit Neuroleptika und Sedativa, die neben anderen unerwünschten Wirkungen das Risiko weiterer kardiovaskulärer und cerebrovaskulärer Komplikationen potenziell erhöhen, behandelt werden. Wenn die Symptomatik als Ausdruck einer psychiatrischen/neurologischen Erkrankung fehlinterpretiert und falsch behandelt wird, können ungerechtfertigte Kosten durch die medikamentöse und nichtmedikamentöse Behandlung, einen längeren stationären Aufenthalt und ggf. ambulante Nachbehandlung entstehen. Aus der Sicht des Patienten kann dieses Phänomen durch die Stigmatisierung zu einer Verunsicherung führen, die sich möglicherweise ungünstig auf die Lebensqualität und den weiteren Genesungsprozess auswirkt.

2.2.2. **Epileptische Anfälle nach Herzoperationen**

Die Beurteilung der Gehirnfunktion fällt bei kritisch erkrankten Patienten auf Intensivstationen häufig schwer, da sedierende Maßnahmen sowie primäre oder sekundäre Hirnschädigungen zu einer Minderung des Bewusstseins bis hin zur Bewusstlosigkeit führen können. Insbesondere die kontinuierliche Elektroenzephalographie (cEEG) über einen längeren Zeitraum bietet die Möglichkeit, bei diesen Patienten die elektrische Aktivität des Gehirns zu beurteilen und so Informationen über den Grundrhythmus, Herdbefunde oder aber epilepsietypische Potentiale zu gewinnen[160]. Epileptische Anfälle treten bei schwer erkrankten Patienten häufig als nichtkonvulsive Anfälle auf und lassen sich rein klinisch daher nur schwer diagnostizieren. Um Patienten mit nichtkonvulsiven Anfällen (non-convulsive seizures, NCS) und anderen pathologischen EEG-Mustern zu identifizieren, empfehlen die „European Society of Intensive Care

Medicine (ESICM)“ und der „European Resuscitation Council (ERC)“ die kontinuierliche EEG-Überwachung bei bewusstlosen Patienten[161,162]. Diese Empfehlungen sind auf Intensivstationen ohne direkte und durchgehende neurologische Expertise allerdings schwierig zu implementieren. Wir untersuchten die Machbarkeit einer kontinuierlichen EEG-Ableitung über mindestens 24h auf einer nicht neurologisch geführten Intensivstation und prüften die Qualität einer automatisierten Analyse in diesem Setting (A4)[117].

In die vorliegende Studie wurden 50 Patienten eingeschlossen, die nach Beendigung der tiefen Sedierung weiterhin bewusstlos blieben. Wir konnten die technische Machbarkeit der cEEG-Aufzeichnung durch einen entsprechend geschulten Arzt und/oder Pflegepersonal mit einer guten Signalqualität während der empfohlenen 24 Stunden nachweisen[117]. Die Analyse des Rohsignals während der Aufzeichnung durch nicht EEG-geschulte Ärzte der Intensivstation war jedoch nicht zuverlässig[117]. Die vorliegenden Daten stützen entsprechende Empfehlungen, dass die Auswertung des cEEG bewusstloser, kritisch kranker Patienten ein EEG-zertifizierter Neurologe mit darüber hinaus spezieller Erfahrung in der Interpretation des cEEG bei Intensivpatienten durchführen sollte[163].

Die Analyse des cEEG ist zeitaufwendig und erfordert Erfahrung, um die Ergebnisse korrekt zu interpretieren. Es wird postuliert, dass die automatische Prozessierung der EEG-Kurven hilft, Veränderungen der Hintergrundaktivität und das Auftreten pathologischer Muster zu erkennen, die dann von einem EEG-Spezialisten weiter analysiert werden können[163]. Dies wurde durch die Beobachtung unterstützt, dass auch Pflegepersonal und Nicht-Neurophysiologen für nicht-konvulsive Anfälle typische Veränderungen im prozessierten cEEG erkennen können[164]. Die vorliegende Beobachtung zeigt, dass bei einer Vielzahl der Patienten die automatisierte Anfallserkennungssoftware korrekterweise keine Anfallsaktivität anzeigte[117]. Bei einer qualitativ guten Ableitung wurde jedoch auch eine relevante Rate falsch positiver (42) und falsch negativer (7) Ergebnisse gefunden. Weitere sechzig falsch-positive Entdeckungen waren auf eine schlechte cEEG-Qualität zurückzuführen, die auch von Nicht-Spezialisten leicht identifiziert werden kann[117]. Die hier eingesetzte automatisierte Anfallserkennung konnte den erfahrenen EEG-Spezialisten nicht ersetzen, aber in Kombination mit einem prozessierten EEG wird die automatische Anfallserkennung leichter entsprechende Patienten und EEG-Muster identifizieren können, die der Beurteilung eines Spezialisten bedürfen.

Die cEEG-Aufzeichnung wird bei Patienten mit einer unvorhergesehenen Bewusstlosigkeit ohne primäre Hirnerkrankungen empfohlen, um nicht-konvulsive Anfälle zu erkennen[161,165], die bei 8% bis 10% dieser Patienten auftreten können[166,167]. In Einklang mit diesen Daten beobachteten wir im Rahmen der vorliegenden Machbarkeitsstudie bei 12% der Patienten (n=6) einer gemischten nicht-neurologischen Intensivpopulation Anfallskorrelate in der cEEG, von denen ein Patient auch klinische Zeichen bot und im Rahmen eines Status generalisierter tonisch-klonischer Anfälle verstarb[117].

Retrospektive Studien zeigen ein vermehrtes Auftreten von Schlaganfällen und einem Delir sowie eine erhöhte Mortalität bei Patienten mit konvulsiven und non-konvulsiven Anfällen nach herzchirurgischen Eingriffen[91,92]. Diese Studien berücksichtigten jedoch entweder klinisch offensichtliche, generalisierte Anfälle oder non-konvulsive Anfälle, die durch eine entsprechende pathologische EEG-Ableitung diagnostiziert wurden, wobei die Indikation zur Durchführung einer solchen Untersuchung unklar bleibt. Insgesamt weisen diese Studien auf eine Inzidenz von postoperativen epileptischen Anfällen von 1-2,5% hin, untersuchten jedoch nicht systematisch die Inzidenz subklinischer Anfälle in der frühen postoperativen Phase. Gofton et al. analysierten ein unselektiertes herzchirurgisches Patientenkollektiv mit einem kontinuierlichen „Subhairline"-EEG und fanden Anfälle bei 3% der Patienten, die sich alle einer Herzoperation unter HLM unterziehen mussten[168]. Die Verwendung von „Subhairline"-Elektroden führt jedoch zu einer Unterdiagnose epileptischer Anfälle[169,170]. Somit lässt sich festhalten, dass die Inzidenz von Anfällen im Rahmen von Herzoperation nach wie vor spekulativ bleibt und wahrscheinlich bisher unterschätzt wurde. Epileptische Anfälle sind jedoch behandelbar und stellen daher ein potentielles Ziel der Prophylaxe von Delir und postoperativen kognitiven Defiziten dar.

Um die genaue Inzidenz konvulsiver und non-konvulsiver Anfälle nach Operationen am offenen Herzen zu bestimmen, führten wir nach Analyse der technischen Durchführbarkeit eine prospektive Untersuchung an konsekutiven Patienten durch, die für eine Herzoperation unter HLM geplant waren (A5)[118]. Wir verwendeten hierzu ein kontinuierliches EEG-Monitoring, dessen 10-Kanal-Registrierung den behaarten Kopf einschloss. Diese Pilotstudie zeigt eine überraschend hohe Prävalenz abnormaler EEG-Muster nach einer offenen Herzoperation. Elektroenzephalografische Anfallskorrelate wurden bei 9/100 (9%), und abnorme EEG-Muster bei 33/100 (33%) der Patienten beobachtet[118]. Für die so detektierten Anfälle fand sich eine signifikante Assoziation mit dem postoperativen Delir und einem höheren Alter. Alle Anfälle verliefen ohne offensichtliches klinisches Korrelat und wurden von ärztlichen und pflegerischen Mitarbeitern der Intensivstation nicht beobachtet. Sie konnten daher nur durch eine umfassende EEG-Überwachung erkannt werden[118].

Wir konnten so erstmalig prospektiv erfasste EEG-Daten einer repräsentativen Population nach offener Herzoperation analysieren[118]. Die Inzidenz elektroenzephalographisch detektierbarer Anfälle scheint höher als in bereits publizierten Studien an Erwachsenen[91,92,168]. Bei neonatalen Patienten, die sich einer Herzoperation unterziehen mussten, wurde eine entsprechende Inzidenz von 8% berichtet[171]. Eine andere Studie, die das EEG bei Sepsis-Patienten untersuchte, berichtete - ähnlich den hier erfassten Daten - ein Auftreten non-konvulsiver Anfälle in 11% und periodischer Entladungen in 25% der erfassten Fälle [172]. Im Prinzip handelt es sich bei der Sepsis um eine systemische Entzündungsreaktion auf einen infektiösen

Erreger, jedoch auch nach einem kardiopulmonalen Bypass wurde bereits eine vergleichbare systemische Inflammation beobachtet[173]. Eine systemische Entzündung könnte daher potenziell ein Faktor sein, der zu abnormalen EEG-Befunden und einem Delir führt. Die vorliegenden Daten bilden die notwendige Grundlage für weitere Untersuchungen bezüglich des Ursprungs und der klinischen Auswirkungen solcher EEG-Pathologien[118].
Diese Studie wurde als Pilotstudie geplant, um die Inzidenz von EEG-Anomalien in der beobachteten Population zu ermitteln. Die vorliegende Fallzahl war nicht ausreichend, um die Zusammenhänge zwischen pathologischen EEG-Mustern und sekundären Zielparametern zu untersuchen[118]. Dennoch fanden wir eine signifikante Assoziation zwischen elektroenzephalographischen Anfällen und einem Delir. Das Delirium trat bei 9% der Patienten auf und war daher wesentlich seltener als die in früheren Studien beschriebene Prävalenz von 24% in der gemischt herzchirurgischen Population[118,174]. Diese Beobachtung lässt sich wahrscheinlich dadurch erklären, dass die Beurteilung des Delirs in der oben erwähnten Untersuchung zu bestimmten Zeiten von speziell geschultem Personal durchgeführt wurde, während sie in dieser Studie im Rahmen der routinemäßigen Patientenversorgung durch (Intensiv-) Pflegepersonal erfolgte, das das Auftreten eines hypoaktiven Delirs, das schwieriger zu identifizieren sein kann, möglicherweise unterschätzt. Non-konvulsive Anfälle und ein Delir traten bei älteren Patienten häufiger auf[118]. Darüber hinaus wiesen Patienten mit elektroenzephalographischen Anfällen vor der Operation tendenziell ein niedrigeres kognitives Niveau (einen niedrigeren MMSE-Wert) auf. Sowohl das Alter als auch eine bereits bestehende kognitive Beeinträchtigung sind bekannte Risikofaktoren für ein Delirium bei Patienten auf der Intensivstation[175]. Es kann diskutiert werden, ob beide Entitäten – epileptische Anfälle und Delir - unabhängige Folgen der Operation für ein gealtertes und möglicherweise bereits vorgeschädigtes Gehirn sein können.

Der Zusammenhang zwischen abnormalen EEG-Mustern und Delirium bei älteren Patienten sollte in weiteren Studien untersucht und um die Erfassung postoperativer kognitiver Defizite erweitert werden. Die Beurteilung dieser Defizite ist zeitaufwendig und stellt hohe Anforderungen an die personellen Ressourcen. Um eine Unterpowerung in POCD-Studien zu vermeiden, ist eine valide Power-Analyse notwendig. Aufgrund des Mangels an robusten Daten zur Häufigkeit von Anfällen in der Population von Interesse, wurde diese Pilotstudie ohne die Erfassung postoperativer kognitiver Leistungsstörungen durchgeführt[118]. POCD ist definiert als postoperativer Leistungsabfall in neuropsychologischen Tests im Verhältnis zur präoperativen Leistung. Die Häufigkeit hängt stark von dem gewählten Follow-up Intervall und den angewandten diagnostischen Kriterien ab[97]. Kognitiv Defizite sind bei 16-23% der Patienten noch drei Monate und bei 31% der Patienten auch noch 3 Jahre nach einer kardialen Bypass-Operation messbar[62,96]. Es ist ebenfalls bekannt, dass Patienten mit einem Status epilepticus oder

wiederholten epileptischen Anfällen auch ein Jahr noch nach dem Ereignis anhaltende kognitive Defizite im Bereich des Gedächtnisses und des Lernens aufweisen[176]. Da epileptische Anfälle potenziell mit Antikonvulsiva behandelbar sind, könnte insbesondere die Erkennung und ggf. Behandlung früher postoperativer Anfälle von großer klinischer Bedeutung für die Inzidenz postoperativer kognitiver Defizite sein. Mit dem Ziel, dies weiter systematisch zu untersuchen, befinden wir uns gegenwärtig in Vorbereitung einer prospektiven, randomisierten und kontrollierten Multicenterstudie.

2.3. Alltagsrelevanz postoperativer kognitiver Defizite

Während neuropsychologische Nebenwirkungen nach herzchirurgischen Operationen als psychometrisch nachgewiesen gelten, blieb die Frage nach ihrem klinischen Wert bzw. der Alltagsrelevanz lange Zeit unbeantwortet. Die durch objektive Leistungstests erfassbaren Defizite fallen in neurologischen Standarduntersuchungen häufig nicht auf, dennoch werden Kliniker oftmals mit subjektiven Aussagen von Patienten- oder Angehörigen konfrontiert, welche auf deutliche Veränderungen hinweisen.

In einer Studie unserer Arbeitsgruppe (COFAS, Cognitive Failure Assessment Survey) erfolgte eine gezielte Exploration der subjektiven Wahrnehmung kognitiver Fehlleistungen nach herzchirurgischen Eingriffen[110]. Erhoben wurde die von Patienten und deren nächsten Angehörigen (>90% Lebenspartner) subjektiv wahrgenommene Einschätzung der kognitiven Leistungsfähigkeit vor und nach Aortenklappenersatz-Operationen mit einem etablierten, leicht modifizierten Fragebogenverfahren (cognitive failure questionnaire, CFQ) sowie deren Korrelationen mit testdiagnostisch objektivierten Defiziten. Die Ergebnisse untermauern die Berichte von Patienten und ihren Angehörigen über wahrgenommene postoperative Veränderungen der kognitiven Leistungsfähigkeiten im Alltag.

In der Auswertung des 3-Monats Follow-Up schien die post-operative Veränderung der kognitiven Leistungsfähigkeit vor allem den nahestehenden Angehörigen (Lebens-/ Ehepartner) aufzufallen; nur ihre Einschätzung der Defizite erreichte statistische Signifikanz. Daher wurde zunächst angenommen, dass die Patienten selbst möglicherweise wenig sensibel in der Wahrnehmung ihrer eigenen kognitiven Leistungseinbußen zu sein scheinen. Eine Annahme, die bereits von Keizer et al. [177] diskutiert und von uns aufgegriffen wurde.

In der anschließenden Follow-Up Untersuchung wurde das klinische Ergebnis der Patienten und die Bewertung durch Angehörige postoperativ nach einem Jahr überprüft (A6)[119]. Während des gesamten Jahres wurden kontinuierlich Patienten rekrutiert, was zu einer Vergrößerung der Fallzahl von ursprünglich 82 auf 108 Patienten (und von 62 auf 85 Angehörige) in der Follow-Up Auswertung führte[119]. In einer erneuten Auswertung zum Zeitpunkt 3 Monate postoperativ zeigte sich, dass durch die fallzahlgebundene Erhöhung der Teststärke, nun auch die

Einschätzung des Leistungsabfalls durch die Patienten selbst statistische Signifikanz erreichte (t(.05; 107) = -2.69; $p < 0.01$, $r = 0.25$). Nach einem Jahr war dieser Unterschied jedoch nicht mehr statistisch signifikant[119]. In einer prospektiven Studie untersuchten Keizer et al.[177] selbstberichtete kognitive Ausfälle bei 81 CABG-Patienten vor und ein Jahr nach der Operation mit dem s-CFQ (CFQ Selbsteinschätzung) und fanden ebenfalls keinen wesentlichen Anteil subjektiver kognitiver Verschlechterung in diesem Setting. Darüber hinaus zeigte die interne Auswertung 112 gesunder Kontrollpersonen im Vergleich zur Patientenkohorte noch mehr kognitive Ausfälle. Gerechtfertigter Weise stellen diese Beobachtungen die Zuverlässigkeit selbstberichteter kognitiver Defizite in Frage. Eine mögliche Ursache hierfür könnte sein, dass psychisch gesunden Probanden im Vergleich zu Patienten mit POCD selbst geringfügige kognitive Defizite bewusster sind, da der kognitive Rückgang selbst einen negativen Einfluss auf die Selbstwahrnehmung und die Fähigkeit, Defizite zu bemerken, haben kann. Darüber hinaus kann das Überstehen potentiell lebensbedrohlicher Krankheiten oder einer lebenswichtigen Operation den Stellenwert der kognitiven Problematik im täglichen Leben verändern und damit zu einer Unterbewertung dieser Defizite führen[177].

Obwohl nahe Verwandte in der Regel wichtige Lebensereignisse und die medizinische Vorgeschichte der Patienten teilen, könnte die externe Evaluation durch sie eine objektivere Beurteilung darstellen und sensibler für alltägliche kognitive Ausfälle mit funktionellen Auswirkungen sein. Daten der COFAS-Studie konnten zeigen, dass POCD drei Monate nach einer Herzoperation mit HLM häufiger und zuverlässiger von nahen Verwandten wie den Ehepartnern wahrgenommen wird[110]. Die Daten des 1-Jahres Follow-up beschreiben, inwieweit mögliche Langzeitbeschwerden auch von nahen Verwandten zuverlässiger wahrgenommen werden und ob ein Zusammenhang mit einem nach drei Monaten psychometrisch gemessenen kognitiven Rückgang besteht[119].

Die Fremdbeurteilung der kognitiven Funktionen verschlechterte sich 3 Monate postoperativ signifikant und blieb im Gegensatz zur Selbsteinschätzung nach einem Jahr tendenziell auf demselben Niveau (p = 0,051). Dies scheint hierbei vor allem einer Verschlechterung der Gedächtnis- und Aufmerksamkeitsfunktionen geschuldet[119]. Bergh et al.[178] untersuchten die externe und interne Wahrnehmung kognitiver Funktionen zwischen 1 und 2 Jahren nach einer CABG-Operation und berichteten, dass Patienten- und Ehegatteneinschätzungen bezüglich Gedächtnisproblemen innerhalb dieses Zeitraums übereinstimmten. Diese retrospektive Studie beinhaltete jedoch weder einen Ausgangsstatus noch eine geeignete neuropsychologische Testbatterie zur Objektivierung kognitiver Beschwerden. Das prospektive Design unserer Studie mit neuropsychologischen Tests und Follow-Up Untersuchungen anhand von Fragebögen ermöglicht sowohl die Korrelation interner und externer Beurteilung als auch die Bewertung ihrer Qualität in Bezug auf messbare Dimensionen der POCD[119]: Die f-CFQ-Bewertung (CFQ Fremd-einschätzung) nach 3 Monaten korrelierte mit schlechteren Ergebnissen in

neuropsychologischen Tests, die das nonverbale Lernen oder die Wortflüssigkeit untersuchten. Es wurde jedoch keine Assoziation zwischen den postoperativen neuropsychologischen „change scores“ nach 3 Monaten und kognitiven Ausfällen gefunden, wie sie von nahen Verwandten ein Jahr nach der Operation wahrgenommen wurden[119]. Sowohl für das 3- als auch für das 12-Monats Follow-up zeigten die s-CFQ-Änderungen keinen Zusammenhang mit den neuropsychologischen „change scores“ 3 Monate nach der Operation[119]. Diese Befunde könnten ein weiteres Indiz dafür sein, dass die POCD im kurzzeitigen Verlauf, d.h. 3 Monate nach der Operation, von den Angehörigen zuverlässiger erkannt wird als von den Patienten. Nach einem Jahr neigten die Angehörigen zwar dazu, die POCD eher zu erkennen als die Patienten selbst, aber dieser Trend erreichte keine statistische Signifikanz. Darüber hinaus konnte durch Korrelationen mit neuropsychologischen Tests nicht nachgewiesen werden, dass diese subjektive Sichtweise eines Angehörigen mit objektiven POCD assoziiert ist[119].

Mehrere Studien stellten einen Zusammenhang zwischen subjektiven kognitiven Defiziten nach einer Herzoperation sowie affektiven Störungen fest und führten dieses Phänomen auf eine zugrunde liegende Depression zurück[179,180]. In unserer Studie zeigte die „Hospital Anxiety and Depression Scale“ (HADS) postoperativ sogar eine Minderung von Depressivität und Angst. Es konnte keine Korrelation zwischen s-/f-CFQ nach 3 und 12 Monaten und dem Ergebnis der HADS nach 3 Monaten objektiviert werden; dies deutet am ehesten darauf hin, dass eine selbst- und fremdbeurteilte Verschlechterung der Gedächtnisfunktion nicht alleine durch diese psychiatrischen Symptome erklärt werden kann[119]. Weitere Untersuchungen, die für Depression und Angst kontrollierten, unterstützen dies[110,111,181].

Nadelson und Kollegen untersuchten den Verlauf der Kognition bei Erwachsenen im Zusammenhang mit kardialen und orthopädischen Operationen sowie der damit verbundenen Anästhesie[182]. Obwohl durchaus kontrovers diskutiert, wurde stellenweise nach einer vorübergehenden postoperativen Verschlechterung auch eine kognitive Verbesserung (postoperative cognitive improvement, POCI) bis zu 12 Monate postoperativ beschrieben – insbesondere, wenn die Operation erfolgreich war und zuvor bestehende Störungen und Beschwerden wie Schmerzen, Entzündungen, Immobilität usw. verbessern konnte. Die Autoren betonen, dass diese Beobachtung auf eine Verbesserung der gesamten kognitiven Fähigkeiten in Summe oder auf eine Verlangsamung bzw. ein Anhalten des präoperativen Rückgangs zurückgeführt werden kann[182]. Obwohl wir an einigen Stellen einzelne Werte mit einer diskreten Verbesserung beobachten konnten, war die vorliegende Studie nicht darauf ausgelegt, POCI systematisch zu erfassen und somit wurde dieser Aspekt nicht separat statistisch ausgewertet[119]. Unter der Voraussetzung, dass chirurgische Eingriffe darauf abzielen, die Lebensqualität der Patienten zu verbessern, sollten zukünftige Studien POCI als einen möglichen postoperativen Verlauf in Betracht ziehen, der wertvolle Ansätze für das Konzept der Salutogenese liefern könnte.

Auch noch über 5 Jahre nach einer Herzoperation konnte man einen Zusammenhang zwischen dem Ausmaß der kognitiven Dysfunktion und der abnehmenden Lebensqualität aufzeigen, wobei ein ähnliches Verhältnis zwischen beiden Messgrößen und den selbstberichteten depressiven Symptomen bestand[99]. Diese Korrelation zwischen dem Schweregrad der POCD einerseits und der Beeinträchtigung der Lebensqualität andererseits war über das gesamte Ausmaß der kognitiven Dysfunktion 1 und 5 Jahre nach der Operation vorhanden[99,183]; sogar relativ geringe postoperative kognitive Defizite schienen hier mit einer verminderten Lebensqualität verbunden. Aus einer patientenzentrierten Perspektive könnte man vorschlagen, dass die POCD als ein Syndrom mit einer kontinuierlichen Schwereverteilung und nicht als ein einfaches dichotomes Merkmal konzeptualisiert und im Hinblick darauf betrachtet werden sollte, wie stark sie subjektiv den einzelnen Patienten beeinträchtigt[24,184]. Obwohl das Fehlen einer spezifischen diagnostischen Schwelle vage erscheinen mag, deckt sich dies mit einer psychiatrischen Sichtweise und den jüngsten internationalen Nomenklaturempfehlungen für perioperative neurokognitive Störungen[185], die fordern, dass neurokognitive Störungen sowohl vor dem Hintergrund objektiver Anzeichen als auch subjektiver Symptome bewertet werden sollten.
Die Tatsache, dass die POCD typischerweise in einer überaus sensiblen Lebensphase auftritt, schnell zum Verlust der Unabhängigkeit führt und die Pflegebedürftigkeit fördert, stellt nicht nur für Patienten und Angehörige, sondern auch für das Gesundheitssystem eine erhebliche Herausforderung dar. Kognitive Funktionen sind ein integraler Bestandteil der menschlichen Selbstwahrnehmung. Folglich übt die entsprechende Beeinträchtigung einen starken Einfluss auf den Alltag aus und stellt ein weitreichendes und tiefgreifendes Handicap dar. Die hier vorliegenden Beobachtungen können dazu beitragen, kognitive Defizite gezielter zu erkennen und damit deren Diagnostik zu verbessern[119]. Möglicherweise legen die Ergebnisse eine Stärkung der Bedeutung Angehöriger im Rahmen der ambulanten und stationären Pflege sowie Forschung nahe, d.h. immer dann, wenn eine möglichst funktionell orientierte und gründliche Erfassung kognitiver Defizite erforderlich ist.

Die vorliegenden Daten zeigen einen beträchtlichen und relevanten subjektiven Einfluss der POCD auf die Funktionen des täglichen Lebens, der sowohl für Patienten als auch für Angehörige wahrnehmbar ist. Im Gegensatz zur Selbsteinschätzung stimmen langfristige Informationen über den kognitiven Rückgang bei Verwandten stärker mit objektiven Messungen überein, was darauf hindeutet, dass sie eine zuverlässigere Quelle darstellen[119]. Unsere Ergebnisse unterstützen die Bedeutung einer kombinierten internen wie externen Bewertung kognitiver Defizite bei der Beurteilung der POCD.

2.4. Behandlung postoperativer kognitiver Defizite: Die INCOGNITO-Studie

Das Auftreten postoperativer kognitiver Defizite, insbesondere nach Herzoperationen, wurde bereits in mehreren Studien untersucht[72,95,97]. Die COFAS-Studie unserer Arbeitsgruppe zeigte, dass diese Defizite von den Patienten und ihren nahen Angehörigen im täglichen Leben deutlich wahrgenommen werden[119]. Über postoperative Behandlungsmöglichkeiten kognitiver Defizite liegen jedoch gegenwärtig keine überzeugenden Daten vor[17].

Mehrere Studien zeigten, dass Patienten mit leichter kognitiver Beeinträchtigung (mild cognitive impairment, MCI) von einem computergestützten kognitiven Training profitieren können[186]. Diese Effekte werden hauptsächlich auf die kognitive/neuronale Plastizität des Gehirns zurückgeführt (d.h. die Fähigkeit des Gehirns, kognitive Funktionen und strukturelle oder funktionelle neurophysiologische Parameter durch Stimulation zu verändern). Als Reaktion auf das kognitive Training weisen ältere gesunde Erwachsene reproduzierbar eine Aktivitätssteigerung in Bereichen der grauen und weißen Substanz auf[187]. Die funktionelle Plastizität hingegen zeigt als Ergebnis des kognitiven Trainings ein gemischtes Muster von erhöhter und verminderter Aktivität in spezifischen Hirnregionen bei älteren gesunden Erwachsenen und eine konsistente Aktivitätszunahme bei MCI-Patienten[187]. Darüber hinaus berichtete eine Studie, die sich der funktionellen Magnetresonanztomographie bediente, über eine erhöhte funktionelle Konnektivität zwischen dem Hippocampus und bestimmten Hirnregionen nach einem effektiven kognitiven Training bei Schlaganfallpatienten [188]. Kognitives Training scheint ebenfalls mit einer Verbesserung depressiver Symptome und der Alltagsfunktionen assoziiert zu sein[189].

Wir stellen hier ein kognitives Training vor, das sich gut in die Standardrehabilitation integrieren lässt, so früh wie möglich stattfindet und darauf abzielt, das Auftreten und die Persistenz kognitiver Defizite kurz- und langfristig zu reduzieren (A7)[121]. Von Interesse ist zudem, ob Patienten mit perioperativ erlittenen Hirninfarkten in unterschiedlichem Ausmaß von dieser Intervention profitieren[121].

Wir entschieden uns bewusst für technisch einfach durchzuführende, Papier-und-Bleistift-basierte Trainingsaufgaben, da die POCD nach kardiochirurgischen Eingriffen hauptsächlich ältere Menschen betrifft[121]. In vielen Studien zur Wirkung des kognitiven Trainings wurden computergestützte Übungsaufgaben verwendet[186], die den Vorteil bieten, Daten einfach, schnell und sehr präzise zu generieren und zu erfassen. Allerdings stellen diese auch heute noch oft ein für ältere Menschen ungewohntes Medium dar, das bei der hier untersuchten älteren Bevölkerung zu Irritation, Berührungsängsten und/oder Frustration führen und somit eine potentielle Verzerrung darstellen könnte. Auf eine Placebo-Intervention für die Kontrollgruppe wurde bewusst verzichtet, da die kognitiven Effekte von Placebo-Interventionen auf die kognitive Leistungsfähigkeit kaum zu kontrollieren sind[121]. Um den Patienten glaubhaft zu suggerieren, dass die Placebo-Intervention einen Einfluss auf ihr Gedächtnis haben könnte, und damit auch

eine Teilnahmebereitschaft zu erreichen, müsste die Struktur der Placebo-Intervention in engem Zusammenhang mit dem kognitiven Training stehen (z.B. Entspannungsübungen, Kreuzworträtsel, Gesprächstherapie, Computerspiele usw.) und könnte somit auch kognitive Trainingseffekte erzielen.

Die bisher einzige prospektive Untersuchung an herzchirurgischen Patienten berichtete über einen positiven Effekt eines Gedächtnis- und Aufmerksamkeitstrainings bei Patienten, die sich einer CABG unterzogen[190], es wurden jedoch keine Informationen über den Einsatz der extrakorporalen Zirkulation in diesem Kollektiv gegeben. In dieser Studie fanden die Übungen zwischen der 6. und der 10. postoperativen Woche statt. Es bestehen gegenwärtig immer noch Unklarheiten bezüglich des optimalen Zeitpunktes und der Dauer der kognitiven Intervention. Es scheint möglich zu sein, dass die Rehabilitation der postoperativ beeinträchtigten kognitiven Funktion durch eine frühere Intervention, d.h. mit einem Beginn innerhalb der ersten Woche, wirksamer ist. Kontrollierte Studien zur Neurorehabilitation von kognitiven Beeinträchtigungen nach einem Schlaganfall haben positive Auswirkungen auf mehrere kognitive Funktionen gezeigt, wenn das restitutive kognitive Training innerhalb von 2 Wochen[191] oder etwa 7 Monaten[188] nach dem Hirninfarkt beginnt. Tiermodelle deuten auf einen zeitabhängigen Anstieg der neuronalen Plastizität (neuroplastisches Fenster) nach cerebraler Ischämie hin, die ihren Spitzenwert bei 7-14 Tagen erreicht und nach 30 Tagen nahezu erloschen scheint. Dennoch ist anzumerken, dass die Übertragbarkeit dieser Befunde vom Labortisch zum Krankenbett schwierig erscheint und das Potential sowie die genaue Ausdehnung des neuroplastischen Fensters beim Menschen noch unklar sind[192].

In unserer Studie wird der Nachweis einer akuten, perioperativen cerebralen Ischämie mittels MRT (inklusive diffusion weighted imaging, DWI) durchgeführt. Akute cerebrale ischämische Läsionen können bei 14%-61% der Patienten nach einer Herzoperation mittels DWI-MRT nachgewiesen werden[35,65]. Die Bedeutung dieser akuten MRT-Läsionen, insbesondere im Hinblick auf die Manifestation einer POCD, bleibt unklar[76]. Nach unserem Kenntnisstand gibt es keine Studien, die Effekte einer periinterventionell erlittenen cerebralen Ischämie kontrollierten. In diesem Zusammenhang scheint es von besonderem Interesse, ob Patienten mit akuter cerebraler Ischämie von einem kognitiven Training in einem anderen Maße profitieren. Bisher wurden verstärkte Anstrengungen zur Prävention der POCD unternommen, die sich auf die Anästhesie, die Kardiotechnologie und die Herzchirurgie beziehen[193], mit begrenztem, aber messbarem Erfolg: Allein diese Präventivmaßnahmen konnten die Inzidenz der POCD in einer Größenordnung von 30% reduzieren[59]. Im Gegensatz zu prozeduralen Präventionsstrategien erlaubt das Konzept des kognitiven Trainings dem Patienten, selbständig, verantwortungsbewusst und aktiv zu handeln. Die so erfahrene Selbstwirksamkeit kann sich zusätzlich positiv auf den Erholungsprozess auswirken[194]. Das Wissen, an einer potenziell lebensbedrohlichen Herzerkrankung zu leiden, deren Symptome und Verlauf nur durch einen großen

operativen Eingriff positiv beeinflusst werden können, ist ein einschneidendes Erlebnis. Es hat sich gezeigt, dass die präoperative Angst ein Prädiktor für eine hohe Morbidität und Mortalität bei Patienten ist, die sich einer Herzoperation unterziehen müssen[195]. Mit dem Wissen, dass kognitive Defizite im Nachhinein aktiv angegangen werden können, kann möglicherweise die Angst vor der Operation reduziert werden.

Die vorliegende Untersuchung enthält sicherlich einige Einschränkungen[121]. Zunächst einmal ist die Teilnahme an der Studie an die Durchführung einer Herzoperation mit einer Herz-Lungen-Maschine gebunden. Ein Vergleich mit Patienten, die sich einer Herzoperation ohne den Einsatz einer extrakorporalen Zirkulation unterziehen, ist daher nicht möglich. Aufgrund fehlender Kenntnisse über den optimalen Startzeitpunkt bzw. die optimale Trainingsdauer kann die Intervention zu früh oder die Dauer von ca. 3 Wochen zu kurz sein. Es kann auch diskutiert werden, ob eine zusätzliche Nachuntersuchung nach mehreren Jahren weitere wertvolle Informationen über den Langzeitverlauf der POCD und die Trainingseffekte liefern würde. Aus den oben genannten Gründen ist in der vorliegenden Studie keine Placebo-Intervention vorgesehen; dies kann die Qualität der Ergebnisse und deren Übertragbarkeit formal einschränken[121].

Die INCOGNITO-Studie (INcreasing COGNItive abilities TO improve patients daily living functions after heart surgery) wird durch die Kerckhoff-Stiftung Bad Nauheim und die Deutsche Stiftung für Herzforschung geförderten. Ihre Ergebnisse könnten potenziell wichtige Auswirkungen auf die Prävention und Behandlung der POCD haben[121]. Insbesondere wenn sich das kognitive Training als wirksam herausstellt, um die Kognition und Lebensqualität zu erhalten oder zu verbessern, könnte es in die Behandlungsprogramme von Rehabilitationszentren integriert werden, die Patienten nach einer Herzoperation behandeln. Ökonomisch und organisatorisch ist dies ohne großen Aufwand möglich, weil die kognitiven Übungen unabhängig voneinander durchführbar sind, keiner kontinuierlichen Kontrolle bedürfen und Rehabilitationszentren in der Regel über Psychologen verfügen, die an der Organisation der Übungen, der Aufgabenverteilung oder der Klärung von Fragen beteiligt sein könnten. Darüber hinaus ermöglicht die Konzeption des kognitiven Trainings auch eine ambulante Durchführung[121].

2.5. Prävention der Hirnschädigung – tierexperimentelle Untersuchungen

Der Hirninfarkt stellt eine gefürchtete Komplikation herzchirurgischer Interventionen dar, da er sowohl mit einer erhöhten postoperativen Morbidität und Mortalität als auch einer reduzierten Lebensqualität assoziiert erscheint[62]. In den vergangenen Jahren wurde eine große Anzahl an pharmakologischen Neuroprotektiva zur Behandlung des Schlaganfalles getestet. Doch während sich viele dieser Verbindungen in Tiermodellen des Schlaganfalls als wirksam erwiesen,

war keine davon in klinischen Studien erfolgreich[80,196]. Eine der Ursachen hierfür scheint zu sein, dass die Auswirkungen neuroprotektiver Wirkstoffe auf die Infarktgröße als zeitabhängig gelten, und die Behandlung oft viel später als in den erfolgreichen experimentellen Schlaganfallmodellen eingeleitet wurde[197]. Präventive pharmakologische Maßnahmen können in der klinischen Situation, in der ein Gefäßverschluss bereits vorliegt, nur schwer ergriffen werden. Im Falle intraoperativ erlittener Hirninfarkte ist hingegen der Zeitraum der Schädigung bekannt. Dies ermöglicht prinzipiell die präventive Gabe potentiell neuroprotektiver Substanzen.

Wir untersuchten die neuroprotektiven Eigenschaften einer Erythropoietin-Gabe vor der experimentellen Induktion eines transienten Mediaverschlusses (MCAO) in der Ratte (A8)[122]. Dosierung (5.000 IE/kg) und intravenöse Applikation wurden entsprechend den Ergebnissen publizierter *in vivo* Studien unter Berücksichtigung der deutlich erniedrigten Blut-Hirn-Schranken Permeabilität dieser Verbindung gewählt[198-200]. Eine multimodale Erfassung der Zielparameter beinhaltete die Magnetresonanztomographie (MRT), Flachdetektor-Computertomographie (fpVCT) und Quantifizierung des Hirnwassergehalts (brain-water content, BWC) mit der Nass-Trocken-Technik[122]. Die raumfordernden Effekte eines Hirnödems wurden durch eine bilaterale Kraniektomie eliminiert[201].

Untersuchungen an Nager-Schlaganfall-Modellen[202-205] deuten darauf hin, dass die Entwicklung eines vasogenen Hirnödems innerhalb der hyperakuten Phase des Schlaganfalls (<6h) einen signifikanten und möglicherweise unterschätzten Einfluss auf die Progression des ischämischen Areals haben könnte, da eine Schwellung des ischämischen Gewebes innerhalb des fixen Schädelvolumens zu einer Beeinträchtigung der Mikrozirkulation im kritisch hypoperfundierten Bereich der Penumbra führen kann. Daher scheinen Kollateralschäden, wie sie durch die raumfordernden Effekte eines großen Mediainfarktes verursacht werden, für bis zu 50% der ischämischen Läsionsbildung verantwortlich zu sein[202]. Therapeutische Maßnahmen, die darauf abzielen, das cerebrale Ödem und den daraus resultierenden raumfordernden Effekt in den frühen Stadien des Schlaganfalls zu reduzieren, können als indirekte oder "sekundäre" Neuroprotektiva wirken[201,202]. Untersuchungen zu den Auswirkungen systemisch verabreichten, rekombinanten humanen Erythropoietins (rhEPO) vor transientem MCAO bei Nagetieren lassen vermuten, dass eine Neuroprotektion eher auf die Minderung des Hirnödems als auf direkte antiapoptotische Effekte zurückzuführen ist[206]. Wir stellten die Hypothese auf, dass EPO, wenn es vor dem transienten MCAO verabreicht wird, seine neuroprotektiven Eigenschaften in der frühen Phase des Schlaganfalls vor allem via sekundäre Neuroprotektion durch Reduktion des Hirnödems ausübt[122].

Es hat sich gezeigt, dass eine Kraniektomie die Mortalität bei Patienten mit großen, raumfordernden territorialen Hirninfarkten signifikant von 71% auf 22% reduzieren kann[207,208]. Experimentelle Studien zur Kraniektomie an einem Nagermodell des MCAO berichten über eine signifikante Reduktion der Infarktgröße, die hauptsächlich auf eine Beseitigung der

mechanischen Kompression zurückzuführen ist[209,210]. Um eine primäre von einer sekundären Neuroprotektion unterscheiden zu können, wurde der ödembedingt erhöhte intrakranielle Druck durch eine bilaterale Kraniektomie vor der transienten MCAO eliminiert[201,202]. Wir erwarteten, dass eine deutliche Ödemreduktion durch Erythropoietin zu ausgeprägten Gruppenunterschieden hinsichtlich Infarktgröße und Ödemvolumen in Abhängigkeit von der Integrität des Schädels führt[122].

Die Vorbehandlung mit rhEPO reduzierte die Größe des ödemkorrigierten Infarkts um etwa 10%[122]. Experimente mit einem vergleichbaren Setting sind rar; zwei Studien an Ratten berichteten keine signifikanten Effekte auf das Infarktvolumen bei einer EPO-Vorbehandlung[206,211]. Im Gegensatz dazu zeigte eine Studie an Mäusen eine Infarktgrößenreduktion von bis zu 47%[212]. Interessanterweise konnte in der vorliegenden Untersuchung eine signifikante Reduktion des Infarktvolumens im Vergleich zur Placebo-Behandlung nur bei intakter Kalotte beobachtet werden[122].

Aus dem Bereich der experimentellen Forschung an Nager-Schlaganfall-Modellen gibt es belastbare Hinweise für die antiödematöse Wirkung von Erythropoietin, die insbesondere auf eine erhaltene Barrierefunktion der Bluthirnschranke (blood-brain-barrier, BBB) zurückgeführt werden kann[213-218]. Eine Untersuchung zu Markern der BBB-Integrität - wie Occludin, alpha- und beta-Catenin - zeigte, dass eine EPO-Behandlung vor und 3 Tage nach einer fokalen cerebralen Ischämie die BBB stabilisieren, ihre Permeabilität verringern und dadurch die cerebrale Inflammationsvorgänge und das Ödem kontrollieren kann[216]. Die Barrierefunktion der BBB hängt hauptsächlich von intakten Endothelzellen und tight junctions ab, die während der Reperfusion nach transienter Ischämie durch die Bildung reaktiver Sauerstoffspezies und Lipidperoxidation einem erheblichen oxidativen Stress ausgesetzt sind[219,220]. Unter dieser Bedingung scheint Erythropoietin die endotheliale Stickoxidproduktion zu stimulieren und kann so einer Reperfusions-vermittelten Schädigung der BBB entgegenwirken[221]. Vor dem Hintergrund, dass sich das Läsionsvolumen proportional zum hemisphärischen Hirnwassergehalt verhält, kann das Volumen des ischämisch infarzierten Gewebes die Ergebnisse von Methoden zur Quantifizierung des Hirnwassergehalts, die ganze Hemisphären einschließen, verzerren; hierzu zählen z.B. die Nass-Trocken-Technik und die Quantifizierung der Mittellinienverlagerung. Das cerebrale Ödem wurde folglich in der vorliegenden Untersuchung mittels MRT unter Verwendung von T2RT-Messungen in bestimmten ROI (regions of interest) untersucht, da sich diese Methode als weitgehend unabhängig von der Läsionsgröße erwiesen hat[204]. Wir konnten eine signifikante Reduktion der Mittellinienverschiebung für die EPO-Vorbehandlung nur in Abwesenheit der Kraniektomie, also bei intakter Kalotte, beobachten. In dieser Gruppe zeigte die MRT T2RT einen Trend zu niedrigeren Mittelwerten für die Behandlungsgruppe mit intaktem Schädel, der allerdings keine statistische Signifikanz erreichte. Dennoch scheinen

diese Daten darauf hinzudeuten, dass die Neuroprotektion der EPO-Vorbehandlung bei transienter MCAO einen starken antiödematösen Effekt impliziert[122].

Wir verwendeten die Flachdetektor-Computertomographie (fpVCT) zur nicht-invasiven dynamischen Bildgebung der cerebralen Perfusion nach temporärer MCAO in kortikalen und subkortikalen Regionen des Infarktes und der gesamten Hemisphäre[222]. Ohne Kraniektomie führte die EPO-Vorbehandlung zu einer signifikanten Erhöhung des cerebralen Blutflusses in kortikalen Regionen des ischämischen Gewebes. In den subkortikalen Bereichen des Infarktes und der gesamten Hemisphäre konnten jedoch keine signifikanten Veränderungen des cerebralen Blutflusses objektiviert werden[122]. Xiong et al. beschrieben die Neuroprotektion durch EPO nach traumatischer Hirnverletzung auch bei EPO-Rezeptor-null-Mäusen und führten diesen Effekt insbesondere auf die Gefäßprotektion zurück[223]. Li et al. untersuchten die Angiogenese bei Mäusen, die 30 Minuten vor und einmal täglich nach einem ischämischen Schlaganfall rhEPO erhielten, und beobachteten zwischen Tag 7 und 21 eine erhöhte angiogene Aktivität; am Tag 14 erreichte der cerebrale Blutfluss prä-ischämische Ausgangswerte[224]. Darüber hinaus führte in einem Kaninchenmodell für Subarachnoidalblutungen intravenös verabreichtes rhEPO zwischen Tag 2 und 16 zu einem signifikant erhöhten cerebralen Blutfluss (CBF)[225]. Zusätzlich zu diesen Beobachtungen der zeitsensitiven Effekte von Erythropoetin zeigten Shafi et al. anhand isolierter Ratten-ACM (A. cerebri media), dass luminal appliziertes EPO die Arterien direkt dilatieren kann und dass eine 24-stündige Vorbehandlung mit EPO diesen Effekt potenziert[226]; nach dieser Vorbehandlung mit einer Einzeldosis EPO und transientem MCAO beobachteten wir nur in umschriebenen, kortikalen Regionen des Infarktes und in Abwesenheit einer Kraniektomie eine signifikante Erhöhung des CBF[122]. Wenn durch die Kraniektomie eine Kompression des Gehirns, der Mikrogefäße und mutmaßlich auch der pialen Arterien sowie Venen reduziert wird, gleicht sich der cerebrale Blutfluss bei EPO- und Placebobehandelten Ratten an. Dies scheint einen lokalen Effekt für das Gebiet des Hirninfarktes zu beschreiben, da unabhängig von EPO-Behandlung oder Kraniektomie keine Unterschiede im cerebralen Blutfluss für die gesamten Hemisphären beobachtet werden konnten[122]. Eine fokale Verbesserung des cerebralen Blutflusses in den kortikalen Regionen des ischämischen Bereichs kann auf eine effizientere Kollateralisierung durch Erythropoietin hinweisen, entweder über antiödematöse und drucksenkende Wirkmechanismen und/oder aufgrund direkter gefäßerweiternder Effekte. Eine verbesserte Kollateralisierung wiederum unterstützt die Erholung kritisch perfundierter, penumbraler Bereiche und somit die Verkleinerung des Infarktkerns, was sich durch eine signifikante Reduktion des ischämischen Läsionsvolumens zeigen ließ[122]. In Übereinstimmung mit den oben genannten Daten zur Infarktgröße und Ödemreduktion konnte letztere nur in Abwesenheit einer Kraniektomie objektiviert werden, d.h. in einer Situation, in der Druckschwankungen vermutlich am stärksten ausgeprägt sind.

Bei der Interpretation der vorliegenden Ergebnisse ist es wichtig zu betonen, dass hier Surrogatparameter für einen sekundären neuroprotektiven Wirkmechanismus berücksichtigt wurden. Diese können als hypothesengenerierend angesehen werden, müssen aber in entsprechenden „mechanistischen" Studien bestätigt werden, um einen direkten oder indirekten Wirkmechanismus objektiv unterscheiden zu können.

In dieser Studie wurde rhEPO verabreicht - ein Präparat, das wegen seiner geringen BBB-Durchgängigkeit in vergleichsweise hohen intravenösen Dosen verabreicht werden muss und mehrere dosisabhängige Nebenwirkungen wie einen erhöhten Hämatokrit und Bluthochdruck sowie prokoagulatorische und prothrombotische Effekte auf die Mikrozirkulation ausüben kann[122]. Diese Nebenwirkungen scheinen in erster Linie auf die erythropoetische Wirkungsweise des EPO-Derivats zurückzuführen zu sein, und es ist prinzipiell denkbar, dass sie das Ausmaß der Neuroprotektion im Zusammenhang mit akuten cerebrovaskulären Erkrankungen begrenzen. Daher wurden in der Vergangenheit Anstrengungen unternommen, die EPO-vermittelte Zytoprotektion zu unterstützen, ohne das hämatopoetische System zu beeinträchtigen. Im Hinblick hierauf konnte gezeigt werden, dass carbamyliertes EPO (CEPO) und Mutanten wie EPO-S100E oder EPO-R103E, vermutlich aufgrund einer veränderten Rezeptorinteraktion, neuroprotektiv wirken, aber keine erythropoetische Aktivität aufweisen. Darüber hinaus besitzt das Fusionsprotein EPO-TAT eine signifikant erhöhte BBB- Durchgängigkeit und ermöglicht so den Einsatz geringerer effektiver Dosen[227,228]. Es bleibt daher zu diskutieren, ob die Verwendung eines anderen EPO-Derivats zu klareren Ergebnissen geführt hätte.

Ein weiterer Aspekt der Pharmakokinetik scheint im Zusammenhang mit der Anwendung von EPO vor der MCAO von besonderem Interesse zu sein. In einem Nagetiermodell einer traumatischen Hirnverletzung wurde nicht nur gezeigt, dass EPO in hohen Dosen verabreicht werden muss, wenn es peripher appliziert wird, und dass die intravenöse Verabreichung der intraperitonealen überlegen ist, sondern auch, dass rhEPO die Blut-Hirn-Schranke mit einer Verzögerung von etwa 4 Stunden überwindet und seine biologische Wirkung nach etwa 8 Stunden zu entfalten scheint [198]. Darüber hinaus wurde berichtet, dass die Halbwertszeit von rhEPO nach einmaliger Injektion zwischen 25,6h und 35,5h liegt[229]. Berücksichtigt man den zeitlichen Rahmen der Pharmakokinetik und den der Ödemdynamik nach Hirninfarkt mit deren Beginn unmittelbar nach der Ischämie, so hätte ein noch früherer Applikationszeitpunkt von rhEPO möglicherweise zu einem ausgeprägteren neuroprotektiven Effekt führen können.

In Bezug auf die Effektgrößen von Infarktvolumen und Perfusionsparametern scheint die Anzahl der Tiere pro Gruppe zwar ausreichend zu sein, doch bleibt fraglich, ob größere Gruppen für Untersuchungen zum Hirnödem zu signifikant unterschiedlichen Ergebnissen geführt hätten. Klinische Tests ergaben keine statistisch signifikante funktionelle Verbesserung, was auf eine begrenzte Sensitivität der klinischen Tests im Allgemeinen oder in Bezug auf die in dieser Studie ausgewählten chronologischen Parameter und Zeitpunkte hindeuten könnte[122]. Zudem

erlaubt das Studiendesign keine Quantifizierung einer möglichen langfristigen Verbesserung. Grundsätzlich können die Verwendung von gesunden Tieren, kontrollierte Laborbedingungen und die Anwendung der Anästhesie die Zuordenbarkeit der Befunde vom Labortisch zum Krankenbett erschweren, was bei der Interpretation der Befunde berücksichtigt werden muss.

Interventionen mit einem erhöhten Schlaganfallrisiko, wie beispielsweise Operationen im kardiovaskulären System, begründen die Diskussion neuroprotektiver Maßnahmen, die dem risikobehafteten Eingriff vorausgehen und auf die Prävention bzw. Reduktion einer potentiellen Hirnschädigung ausgelegt sind. Diese Studie zeigt, dass eine Einzeldosis von rhEPO, die vor dem transienten MCAO bei Ratten verabreicht wird, das ischämische Läsionsvolumen signifikant reduziert, die Mittelinienverlagerung verringert und den lokalen cerebralen Blutfluss in den kortikalen Regionen der Ischämie nach 24 h erhöht[122]. Die Daten deuten möglicherweise auf eine Interaktion zwischen durch EPO vermittelten ödem- und druckreduzierenden Mechanismen sowie blutflusssteigernden Effekten hin[122].

3. Zusammenfassung und Ausblick

Die vorliegende kumulative Habilitationsschrift untersucht pathophysiologische Aspekte der Hirnschädigung während herzchirurgischer Eingriffe. Darüber hinaus werden anhand tierexperimenteller und klinischer Methoden unterschiedliche, bisher vielleicht weniger bekannte, klinische Erscheinungsbilder diskutiert und mögliche therapeutische sowie präventive Ansätze aufgezeigt.

Gasförmige Embolien treten regelmäßig während herzchirurgischer Eingriffe unter Einsatz der Herz-Lungenmaschine auf und scheinen einen wesentlichen sowie viel diskutierten Einfluss auf das Entstehen einer cerebralen Schädigung auszuüben. In den entsprechenden Tiermodellen ließ sich das Volumen dieser Embolien bisher weder zuverlässig messen noch kontrollieren. Mit einem von unserer Arbeitsgruppe entwickelten Rattenmodell der cerebralen Luftembolisation konnten wir die zuverlässige Produktion gasförmiger Emboli mit unterschiedlichen, definierten Durchmessern demonstrieren (A2). Eine direkte Abhängigkeit der Schlaganfallhäufigkeit und -schwere von dem Durchmesser der Luftembolien konnte in unserem Experiment nicht belegt werden[115].

Die häufigsten klinischen Korrelate einer Hirnschädigung während herzchirurgischer Eingriffe stellen Hirninfarkte, das Delir und postoperative kognitive Defizite dar[72]. Im Rahmen der eigenen klinisch-neurologischen Tätigkeit wurden wir auf das vermehrte Auftreten optischer Halluzinationen nach diesen Operationen aufmerksam, die bis zu diesem Zeitpunkt in der Literatur kaum Erwähnung fanden. Zum einen stellten wir exemplarisch Art, Umstände und den Verlauf dieser Symptomatik anhand dreier Beispiele dar (A3)[116]. Zum anderen konnten wir anhand einer Screeninguntersuchung andeuten, dass dieses Phänomen durchaus häufig (11/100) auftritt und bis dato vielleicht unterschätzt wurde (A3)[116]. Betroffene Patienten sind sehr beunruhigt; fehlende Hinweise auf einen Zusammenhang der Halluzinationen mit akut zu behandelnden neurologisch/ psychiatrischen Erkrankungen und das spontane Sistieren der Symptome unterstreichen einerseits die Bedeutung einer frühzeitigen Aufklärung des Betroffenen. Andererseits bietet die Kenntnis dieser Entität eine Möglichkeit, nicht gerechtfertigte medikamentöse Therapien mit Neuroleptika oder Sedativa, deren entsprechende Nebenwirkungen, Kosten und auch eine Stigmatisierung zu verhindern. In einem nächsten Schritt erfolgt gegenwärtig eine strukturierte, prospektive Untersuchung postoperativer optischer Halluzinationen, um belastbarere Aussagen über ihre Inzidenz und Ätiologie sowie potentielle Risikofaktoren zu erhalten.

Die gegenwärtige Literatur beschreibt weiterhin epileptische Anfälle nach herzchirurgischen Operationen, die das Risiko eines postoperativen Delirs und postoperativer Schlaganfälle zu erhöhen sowie eine erhöhte Mortalität zu bedingen scheinen[91,92]. Der Mangel an adäquaten technischen Mitteln lässt den Schluss zu, dass in entsprechenden Studien bisher die Inzidenz dieser Anfälle unterschätzt wurde. Wir konnten die Machbarkeit einer kontinuierlichen EEG-

Ableitung über mindestens 24 Stunden postoperativ auf einer nicht-neurologischen Intensivstation belegen (A4)[117]. In einer Pilotstudie fanden wir eine überraschend hohe Inzidenz pathologischer EEG-Muster (33%) und elektroenzephalographisch detektierbarer epileptischer Anfälle (9%) nach elektiven, offenen Herzoperationen (A5)[118]. Da letztere mit dem Auftreten eines Delirs assoziiert erschienen, können diese Erkenntnisse als ein relevantes Phänomen interpretiert werden. Gegenwärtig ist eine prospektive, kontrollierte Multicenterstudie in Planung, die die präventive antikonvulsive Therapie zur Verminderung postoperative kognitiver Defizite in dieser Population untersucht (Prevention of Seizures after Cardiac Surgery to Reduce Posteroperative Cognitive Deficits, ReCog Trial).

Das prinzipielle Auftreten persistierender kognitiver Defizite in der Herzchirurgie scheint unumstritten - traditionsgemäß werden solche Hirnleistungsstörungen von neuropsychologischen Testbatterien erfasst. Ob, wie lange und in welchen Bereichen so aufgedeckte Störungen im Alltag von Patienten selbst oder von nahestehenden Angehörigen registriert werden, war bisher nicht ausreichend untersucht. Unsere Arbeitsgruppe konnte im Rahmen der COFAS-Studie zeigen, dass POCD einen messbaren Einfluss auf den Alltag der Patienten ausübt, der auch von Nahestehenden wahrgenommen wird. Hierbei scheint die Fremdeinschätzung, vor allem im Langzeitverlauf, besser mit objektiven Testergebnissen zu korrelieren und stellt womöglich ein zuverlässigeres Instrument zur differenzierten Erfassung dieser Störungen dar (A6)[119]. Diese Ergebnisse betonen darüber hinaus den Stellenwert einer kombinierten internen und externen Evaluation von POCD.

Seit der ersten Beschreibungen postoperativer kognitiver Defizite wurden vermehrt präventive Maßnahmen untersucht, deren Nutzen sich schlecht bestimmen lässt[120]. Obwohl davon auszugehen ist, dass trotz dieser Anstrengungen circa die Hälfte der herzchirurgischen Patienten von POCD betroffen sind, liegen keine befriedigenden Daten zur Behandlung dieser Störungen vor. Das Design der INCOGNITO-Studie ermöglicht die Untersuchung des therapeutischen Nutzens eines kognitiven Trainings, das sich leicht in den Ablauf der postoperativen Rehabilitation integrieren lässt (A7)[121]. Hierbei wird ein besonderer Fokus auf die Reduktion postoperativer kognitiver Defizite und einer möglicherweise damit verbundenen Verbesserung der Lebensqualität und dem Erhalt der Selbstständigkeit gelegt.

Im Hinblick auf die Entwicklung pharmakologischer Neuroprotektiva verlief die Übertragung verheißungsvoller Ergebnisse von der Laborbank an das Krankenbett trotz der Investition enormer finanzieller und personeller Ressourcen bisher frustran[80]. Insbesondere bei akuten, unvorhersehbaren Hirnerkrankungen erscheint der Applikationszeitpunkt als ein besonders kritischer Faktor. Die Tatsache, dass der Zeitraum einer Hirnschädigung während herzchirurgischer Interventionen bekannt ist, eröffnet hier prinzipiell die Möglichkeit, die präventive Gabe potentiell neuroprotektiver Substanzen zu untersuchen. Unsere Arbeitsgruppe konnte an einem Tiermodell des ischämischen Schlaganfalles zeigen, dass bereits die einmalige

Vorbehandlung mit Erythropoietin die Infarktgröße reduzieren und den lokalen cerebralen Blutfluss erhöhen kann (A8)[122]. RhEPO scheint dabei indirekt neuroprotektiv, durch Senkung des ödemvermittelten Druckes zu wirken[122].

Die Verbesserung kognitiver Funktionen nach einer Herzoperation ist komplex und stellt eine große Herausforderung dar. Das Gehirn gilt weithin als eines der komplexesten Organe des menschlichen Körpers mit signifikanten anatomischen und funktionellen interindividuellen Unterschieden[230,231]. Die Optimierung neurologischer Funktionen nach herzchirurgischen Eingriffen erfordert daher wahrscheinlich interdisziplinäre, individualisierte und patientenzentrierte Ansätze, die an den unterschiedlichen Determinanten der Gehirnfunktion, wie der Sauerstoff- und Glukosezufuhr, dem cerebralen Perfusionsdruck bis hin zur sorgfältigen pharmakologischen Modulation der Aktivität neuronaler Netzwerke, der chirurgischen Stressantwort und der daraus resultierenden Entzündungsreaktion ansetzen. Ein wichtiges Ziel wird sicherlich die Entwicklung gebündelter Protokolle sein, die darauf abzielen, mehrere intra- und postoperative Variablen gleichzeitig und praktikabel zu optimieren, um die postoperative kognitive Funktion älterer Patienten zu fördern[17]. Die bisher erzielten Fortschritte in diesen Bereichen und das Potenzial bestehender kognitiver neurowissenschaftlicher Ansätze zur Untersuchung und Behandlung dieser Probleme stimmen optimistisch, dass es gelingen wird, die postoperative neurologische Funktion älterer Herzchirurgie-Patienten in Zukunft weiter zu verbessern.

4. Eigene Originalarbeiten

4.1. Inter- and intra-rater reliability of computer-assisted planimetry in experimental stroke research (A1).[114]

Tobias Braun, Jan Pukropski, Mesut Yeniguen, Jasmin El-Shazly, Markus Schoenburg, Tibo Gerriets, Manfred Kaps, Marlene Tschernatsch, Martin Juenemann

Die computergestützte Planimetrie wird in der experimentellen Schlaganfallforschung häufig verwendet, um wichtige Zielgrößen, wie das Ausmaß einer ischämischen Läsion oder das hemisphärische Volumen, zu bestimmen. Es liegen allerdings nur unzureichende Daten über die Länge der Übungsphase des Untersuchers vor, die erforderlich ist, um eine ausreichende Reliabilität in der Planimetrie zu erreichen.

Die computer-gestützte Planimetrie wurde über einen Zeitraum von 15 Monaten von zwei verblindeten Untersuchern durchgeführt, die zunächst in dieser Methode unerfahren waren. Zur Bestimmung der inter-rater Reliabilität wurde das hemisphärische und läsionale Volumen von 227 männlichen Wistar-Unilever-Ratten nach experimentellem Verschluss der A. cerebri media in diffusions- und T2-gewichteten Sequenzen bestimmt. Zur Ermittlung der intra-rater Reliabilität beurteilte ein Untersucher das hemisphärische und läsionale Volumen in 87 T2-gewichteten Sequenzen zweimalig innerhalb eines Intervalls von sechs Wochen. Die Korrelation wurde mithilfe von Krippendorffs Alpha errechnet, Bland-Altman-Plots illustrierten die Übereinstimmung.

Die inter-rater Reliabilität nahm in den ersten sieben Wochen zu und blieb auf vergleichbar hohen Werten (Krippendorffs Alpha>0,88). Für die intra-rater Reliabilität betrug der Alpha-Wert von Krippendorff 0,84 für hemisphärische und 0,85 für das Läsionsvolumen. Der Bland-Altman-Plot zeigte in Abwesenheit systematischer Fehler eine solide Übereinstimmung der Bewerter.

Vereinfachte geometrische Modelle oder automatisierte Methoden für die Planimetrie können prinzipiell zur Bestimmung des Läsionsvolumens verwendet werden, sind zur Beurteilung des hemisphärischen Volumens jedoch ungeeignet. Die computergestützte Planimetrie kann eine geeignete Methode sein, um das hemisphärische oder läsionale Volumen bei Nagetieren zu messen, erfordert jedoch eine ausreichend lange Lernphase von etwa zwei Monaten. Selbst ein erfahrener Untersucher kann hier dennoch Daten mit deutlichen Abweichungen erzeugen.

Inter- und intra-rater-abhängige Abweichungen sowie eine ausreichend lange Übungsphase sollten bei der Planung und Durchführung experimenteller Studien berücksichtigt werden.

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Short communication

Inter- and intra-rater reliability of computer-assisted planimetry in experimental stroke research

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ABSTRACT

Background: Computer-assisted planimetry is widely used in experimental stroke research to assess the size of the ischemic lesion or hemispheric volume.
New method: Only insufficient data exist on the training required to achieve sufficient reliability in planimetry. Therefore, planimetry was performed over 15 months by two blinded raters who were initially inexperienced in the method. For inter-rater reliability, the hemispheric and lesional volume of 227 male Wistar Unilever rats subjected to middle cerebral artery occlusion were determined in diffusion- and T2-weighted sequences. For the intra-rater agreement, one investigator assessed the hemispheric and lesional volume in 87 T2-weighted sequences twice within a six-week interval. The correlation was calculated using Krippendorff's alpha and Bland-Altman plots illustrated the agreement.
Results: Inter-rater agreement increased during the first seven weeks and remained at high values (Krippendorff's alpha > 0.88). For intra-rater agreement, Krippendorff's alpha was 0.84 for hemispheric and 0.85 for lesional volume. The Bland-Altman plot indicated solid agreement between raters in the absence of systematic errors.
Comparison with existing methods: Simplified geometrical models or automated methods for planimetry can be used to determine lesional volume, but both approaches are inappropriate to assess hemispheric volume.
Conclusion: Computer-assisted planimetry can be an appropriate method to determine hemispheric or ischemic lesion volume in rodents but requires a sufficiently long learning period of approximately two months. Even an experienced investigator can generate data with serious variation. Inter- and intra-rater-dependent bias should be considered during the design and performance of respective studies.

1. Introduction

Computer-assisted planimetry is a widely established tool that is used to determine hemispheric volume (HV) or ischemic lesion volume in experimental stroke research. For the assessment of clinical deficits, scaled sensomotoric tests for different deficits, or rather global tests, such as the rotarod test, are often used. However, the clinical evaluation of animals often proves impractical and due to the fact that a blinded, trained tester is needed; those tests are often prone to subjectivity and variation. For example, a test in which a reflex-paw placement is elicited by touching the ipsilateral vibrissae on a hard surface may be complicated in mice due to the animal's resistance to being positioned in such a way, resulting in variability and unreliable assessments due to animal mobility, temperament or motivation (Kahle and Bix, 2012). Another problem is the fact that some deficits – neglect, for example - might be hard to detect or might develop over time (such as post-stroke dysphagia) (Sugiyama et al., 2014). In contrast, the size of an ischemic lesion seems to be less affected by confounding factors, and, therefore, ischemic lesion volume is often used as a robust primary endpoint for the assessment of therapeutic efficacy (Kahle and Bix, 2012).

Computer-assisted planimetry can be applied in computed tomography, magnetic resonance (MR) or histological staining techniques, such as tetrazolium chloride staining (Okuno et al., 2001; Sims et al., 2009). Based on the Cavalieri principle, a set of two-dimensional, parallel slices of an object with known thickness is needed. To calculate the volume of the object, the area of each slice is determined manually.

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Then, the areas are added and multiplied by the thickness of the slices (Roberts et al., 2000). Geometric approaches – e.g., ellipsoid or spherical models – can be used to estimate infarct size as well, but these formulae tend to over- or underestimate the true volume (Sims et al., 2009).

Our investigation was conducted to assess the inter- and intra-rater reliability of planimetry in stroke-related experimental MR imaging.

2. Methods

To calculate inter- and intra-rater reliability, we prospectively assessed imaging data in experimental stroke research in our own research group over 15 months. All procedures were conducted in accordance with our institutional guidelines and the German animal protection legislation and were approved by the regional ethics committee (Regierungspraesidium Darmstadt: V54-19c 20/15-B2/170; V54-19c 20/15-B2/144).

For inter-rater reliability, HV and lesional volume (LV) of a total of 227 male Wistar Unilever rats (HsdCpb:WU; Harlan Winkelmann, Germany) were determined in diffusion-weighted (DWI) and T2-weighted sequences. In short, imaging was performed using a seven Tesla MRI device (Bruker PharmaScan 7.0 T, 16 cm). Overall, 214 DWI sequences and 278 T2-weighted sequences were analysed in this manner.

All animals were subjected to middle cerebral artery occlusion (MCAO) using the suture model (Koizumi 1986): Prior to surgery, each rat was administered 100 mg/kg metamizol (Novalgin®, Sanofi, Germany) orally. Anaesthesia was administered with 5% isoflurane delivered in air at 3.0 L/min and maintained during surgery via a facial mask with 2–3% isoflurane delivered in air at 0.5 L/min. Body core temperature was recorded with a feedback-controlled heating pad and kept at 37.0 °C (± 0.25 °C) during surgery and imaging procedures. After local anaesthesia (2% lidocain [Xylocain®, AstraZeneca, Germany]), MCAO was performed. In brief, the right common carotid artery was exposed, and a silicone-coated nylon suture (4-0) was inserted. Then, the occluder was advanced proximally until its tip reached the anterior cerebral artery beyond the carotid bifurcation, thus blocking the blood flow to the right middle cerebral artery. Metamizol was administered orally again 6 h after the first application and applied to the tap water for the remaining survival time of 24 h.

Computer-assisted planimetry of the ischemic lesions and total HV was performed by two blinded investigators who had just learned this technique using the image analysis software Image J 1.25 s (National Institutes of Health, USA) (Schneider et al., 2012). First, contrast and brightness were adjusted in such a way that the borders of anatomical structures and the hyperintense ischemic lesions were clearly distinguishable. Afterwards, the edges of the hemispheres and the hyperintense ischemic lesions were traced manually on each slice using a handheld mouse and neuroanatomic landmarks (Fig. 1, a). The areas were then added and multiplied by the slice thickness to calculate corresponding volumes. Planimetry was demonstrated to the investigators once; they then performed planimetry three times under the supervision of an experienced user. Furthermore an example selection of MRI images displaying ischemic lesions, intracerebral haemorrhage, subarachnoidal haemorrhage and different artefacts (e.g., partial volume effects, ghosting or aliasing) was demonstrated to the raters. If these artefacts were judged by both investigators as severe and potentially impeding identification of lesion edges (e.g., missing parts of a hemisphere or lesion due to the artefact), corresponding images were excluded from the study. The training session lasted a total of 90 min. Because both investigators were new to planimetry, learning curves could be generated over the course of 15 months. For intra-rater agreement, one blinded investigator, with at least 18 months of experience in planimetry, examined the HV and LV in 87 T2-weighted sequences twice over a six-week interval.

Statistics were calculated using SPSS Version 19.0 for Windows (Armonk, NY: IBM Corp.). Inter- and intra-rater correlation was assessed with Krippendorff's alpha using an SPSS macro (http://www.afhayes.com/public/kalpha.sps). Krippendorff's alpha is a correlation coefficient ranging between -1 and +1. A value of +1 implies total agreement, whereas 0 implies no agreement. In nominal- and ordinal-scaled data, a Krippendorff's alpha of -1 can be achieved when the investigators form a contrary opinion, implying high reliability (Hayes and Krippendorff, 2007).

The Bland-Altman plot, a graphic tool based on a coordinate system, was used for each sequence and in HV and LV to visualize and estimate the true value, systematic errors and agreement, respectively (Bland and Altman, 1986). The average of the paired values (on the x-axis) was plotted against their difference (on the y-axis). The average was used, as it fluctuates around the true value, providing its best estimation. The mean of all measurements was plotted on the coordinate system using a horizontal line. Additionally, the limits of agreement (limits of agreement = average ± 2 * standard deviation) were added. The distribution of data points indicates systematic errors (Bland and Altman, 1986; Grouven et al., 2007).

3. Results

During the first seven weeks, planimetry was performed in 142 MRI sequences twice by each rater (89 T2-weighted & 53 DWI). The remaining analyses – i.e., 350 sequences for each rater – were evenly spread over the course of 60 weeks. All images analysed for this study were free of relevant artefacts. Both raters completed the same number of analyses at the same frequency and delayed those analyses only by a few hours. Krippendorff's alpha for inter-rater agreement over the course of 15 months for HV and LV in T2-weighted and DWI sequences reached their highest values, meaning in the highest agreement, after seven weeks (Fig. 1b).

Table 1 lists the means and limits of agreement used to calculate the Bland-Altman plots. Fig. 1c shows an exemplary Bland-Altman plot for the HV measured in T2-weighted sequences. Because Krippendorff's alpha reached its highest value after a training period of seven weeks, the values from the first seven weeks were removed, resulting in 82 T2-weighted and 108 DWI sequences; the plots were recalculated from the remaining data (Fig. 1d).

Table 1 depicts the values used in the Bland-Altman plots. The means of all differences were calculated. The limits of agreement were then calculated using the formula "mean of differences + 1.96 x standard deviation" for the upper limit and the formula "mean of differences – 1.96 x standard deviation" for the lower limit. The width of the limits of agreement can be used to estimate the extent of agreement.

4. Discussion

The use of computerised procedures in experimental stroke research suggests a certain degree of objectivity, but nevertheless, during the process of data acquisition, examiner dependence has to be assumed. Herein, we investigated if rater-dependent variations exist in computer-assisted planimetry.

This analysis showed that inter-rater agreement reached a high level of agreement after approximately two months or 284 examined MRI sequences and remained stable over the course of 15 months of observation (Fig. 1b, Krippendorff's alpha > 0.88). Because both investigators used the same technique and measured the same data, a strong correlation was expected (Grouven et al., 2007). However, a strong correlation cannot necessarily be equated with strong agreement. We therefore used the gold standard when assessing agreement: the Bland-Altman plot (Bland and Altman, 1986).

The Bland-Altman plots showed smaller limits of agreement when data from the learning period of seven weeks were excluded (Table 1, Fig. 1c + d). Any variation observed during this period revealed no relationship with the volume measured. All Bland-Altman plots showed

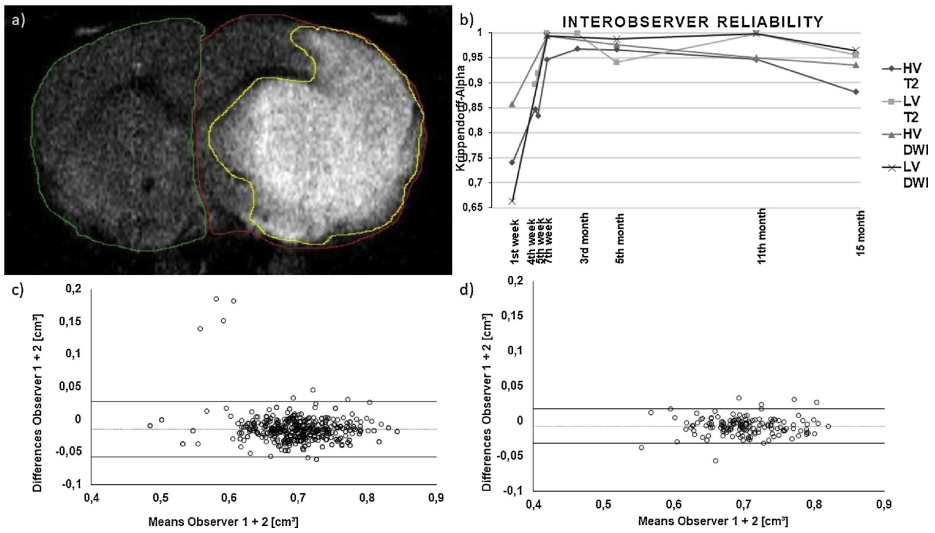

Fig. 1. a) Computer-aided planimetry, T2-weighted MRI image. The yellow line traces the ischemic lesion, the red line traces the ipsilateral hemisphere and the green line traces the contralateral hemisphere b) Inter-rater agreement is expressed as Krippendorff's alpha over the course of 15 months for HV and LV in T2-weighted and DWI sequences, respectively. Krippendorff's alpha reached the highest value – i.e., the strongest agreement – after seven weeks. Finally, c) and d) show two exemplary Bland-Altman plots. c) The complete data set for HV in T2-weighted images. d) Data from the first seven-week period were removed, visualising a considerable narrowing of the limits of agreement. Further Bland-Altman plots are not presented, because they showed similar results.

Table 1
Calculated Values for the Bland-Altman Plots.

Intra-rater	Mean of differences [cm³]	Limit of agreement [cm³]	
		Upper	Lower
HV T2-weighted sequences	−0.006	0.094	−0.107
LV T2-weighted sequences	0.006	0.110	−0.096
HV T2-weighted sequences incl. the first 7-week period	−0.015	0.028	−0.058
HV T2-weighted sequences w/o the first 7-week period	−0.006	0.017	−0.031
HV Diffusion-weighted sequences incl. the first 7-week period	−0.006	0.051	−0.064
HV Diffusion-weighted sequences w/o the first 7-week period	−0.004	0.038	−0.029
LV T2-weighted sequences incl. the first 7-week period	−0.001	0.072	−0.074
LV T2-weighted sequences w/o the first 7-week period	0	0.014	−0.014
LV Diffusion-weighted sequences incl. the first 7-week period	−0.001	0.067	−0.063
LV Diffusion-weighted sequences w/o the first 7-week period	−0.002	0.015	−0.021

similar results for HV or LV in T2-weighted and DWI sequences. In all plots, the scatter of points did not suggest a systematic error such as large differences for small lesion size (cloud-shaped scattering in upper left corner) or large lesion size (cloud-shaped scattering in upper right corner).

Due to the observation that intra-rater agreement was less than inter-rater agreement, we hypothesize that even an experienced investigator can generate data with serious variations that must be considered during the study design and interpretation of planimetric data. An alternative interpretation might indicate an investigator's poor planimetry skills, although he had approximately 18 months of experience using planimetry.

Limited data exist on the inter- and intra-rater reliability of planimetry in experimental stroke research. Nagel and co-workers demonstrated good intra-rater reliability when using planimetry with MRI sequences. The reliability, when assessing the LV, was dependent on the time lag between MCAO and MRI, with a higher variability after 5 h from MCAO compared to 3, 8 or 12 h from MCAO. The variability of HV was lower and not time-dependent. However, the authors did not report on the experience of the rater (Nagel et al., 2004). Friedländer and co-workers reported a lower reliability of planimetry compared to an ImageJ macro when using triphenyltetrazolium chloride staining. In this investigation, the results of 15 students "who were all familiar with […] ImageJ-based free-hand planimetry" were compared to the aforementioned macro. They did not indicate their time of training or expertise (Friedländer et al., 2017). Bråtane and co-workers reported a higher correlation when ischemic lesions on MRI images were determined by an experienced investigator rather than by an unexperienced investigator. Furthermore, the results showed better agreement when apparent diffusion coefficient (ADC) images were used instead of DWI images. The limits of agreement ranged from -42.4 to 62.1 mm³ (ADC) and from -71.1 to 125.5 mm³, which are larger than our values after the training period (Bråtane et al., 2009). This further supports the value of sufficient training.

Our data suggest that computer-assisted planimetry can be an appropriate method with which to determine HV or ischemic lesion volume in rodents, but it requires a sufficiently long learning period. A training period of approximately two months, including the analysis of

approximately 280 images, should be included in the experimental design. However, even after this learning period, the method remains prone to rater-dependent, systematic errors. In our experience, this is mostly due to different contrast parameters, especially along the border of the ischemic lesion and healthy brain tissue, and small variances when tracing the edges of an object using a handheld mouse, leading to deviations as a result of error propagation. When designing an experimental stroke trial, sufficient time should be allowed in advance for appropriate training of the rater, with images from past studies. A thoroughly conducted training of the raters should lead to smaller deviations and thus might facilitate smaller sample sizes. However, our study was not powered to address this issue.

Evaluating the validity of planimetry in experimental stroke research is hard to realise because there is no gold standard by which to quantify the exact volume of the hemisphere or ischemic regions, respectively. The HV can be quantified by its water displacement using Archimedes' principle. However, a transfer of this method to the irregularly and inhomogeneously shaped ischemic lesion is difficult. Because a means by which to test the validity of this method is hard to realise, we did not pursue this matter.

A different approach for volumetry is Euclidean geometry. Here, LV is approximately calculated using simple geometric models (sphere, ellipsoid, cylinder). Those models tend to over- or underestimate the true volume of the lesion. The spherical model seems to achieve the best results compared to planimetry (Sims et al., 2009). However, as mentioned before, ischemic lesions are usually shaped irregularly, so these models seem to oversimplify. Although it seems acceptable to use a spherical model for correspondingly shaped ischemic lesions, the shape of the ischemic lesion is usually – in our opinion – far too different from geometric models. In human stroke, the irregular form was demonstrated by Asdaghi et al. (Asdaghi et al., 2014).

Moreover, different automated methods for volumetry exist: LV can be measured using ADC thresholding. By defining an ischemic threshold of the ADC, an automated program can define the ischemic volume using these values on the MRI sequence (Meng et al., 2004). Alternatively, autotracing techniques have been evaluated that use grey values in MRI-images (Nagel et al., 2004). Both methods are fast, automated, and user-independent. However, they cannot be used when trying to assess the HV.

In summary, planimetry is a reliable approach for volumetry that requires sufficient training. When assessing LV, automated approaches seem to be a user-independent option by which to assess HV; there does not seem to be an alternative for planimetry. As such, sufficient skills and training in planimetry are needed in experimental stroke research. Minimisation of inter-rater-dependent bias in investigation with multiple arms could be achieved by using one single rater for all data or, if multiple raters are required, by an equal allocation of the different study groups. However, researchers must remember that even an experienced rater will, to some extent, generate data with serious variation. Computer-assisted planimetry is a fast method that could be even faster or even more accurate when using a stylus-based graphical tablet or a touch screen-based system. Further investigations may address this approach.

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Disclosure of potential conflicts of interest

The authors declare that they have no conflict of interest.

Research involving animals

All applicable international, national, and institutional guidelines for the care and use of animals were followed. All procedures were conducted in accordance with our institutional guidelines and the German animal protection legislation and were approved by the regional ethics committee (Regierungspraesidium Darmstadt: V54-19c 20/15-B2/170; V54-19c 20/15-B2/144).

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4.2. Impact of bubble size in a rat model of cerebral air microembolization (A2).[115]

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Cerebrale Luft-Mikroembolisationen (cerebral air microembolization, CAM) sind eine häufige Nebenwirkung diagnostischer oder therapeutischer Interventionen. Neben der Reduktion der Embolienanzahl könnten im klinischen Alltag gebräuchliche Filtersysteme auch zu einer Dispersion großer Gasblasen und damit zu einer Vergrößerung der Kontaktfläche von Gas, Flüssigkeit und Endothel führen. In dieser Untersuchung evaluierten wir Produktion und Applikation von Luft-Mikroembolien unterschiedlicher Durchmesser in einem Rattenmodell der CAM und erfassten das funktionelle Ergebnis sowie das Infarktvolumen im Verhältnis zum Blasendurchmesser.

Hierzu wurden Luftbläschen von definierter Anzahl und Durchmesser in die A. carotis von Ratten injiziert. Gruppe I (n = 7) erhielt 1800 Luftblasen mit einem Durchmesser von 45 µm, Gruppe II (n = 7) 40 Blasen von 160 µm sowie die Kontrollgruppe (n = 6) Kochsalzlösung ohne Gasblasen; Gruppen I und II wurde mit insgesamt 86 nl das gleiche Gesamtvolumen an Luft injiziert. Das funktionelle Ergebnis wurde mittels Neuroscore und dem Rotarod-Test zu Beginn, nach 4 h und 24 h beurteilt, anschließend erfolgten die cerebrale Magnetresonanztomographie sowie die Berechnung der Infarktgrößen.

Die computergestützte Auswertung der Blasendurchmesser zeigte eine hohe Konstanz mit geringer Standardabweichung (Gruppe I: 45,83 µm± 2,79; Gruppe II: 159 µm± 1,26). Die Tiere in Gruppe I und II erlitten Hirninfarkte mit konsekutiven klinischen Defiziten ohne signifikante Unterschiede. Die Infarktgrößen unterschieden sich zwischen den beiden Gruppen ebenfalls nicht signifikant (p = 0,931 u-Test).

Wir stellen hier ein Tiermodell vor, das sowohl zuverlässige als auch kontrollierte cerebrale Luftembolien mit unterschiedlichen Blasendurchmessern ermöglicht und neurologische Defizite in Folge einer einseitigen Hirnschädigungen hervorruft. Unsere Ergebnisse wiesen nicht auf eine direkte Abhängigkeit der Schlaganfallhäufigkeit und -schwere von dem Durchmesser der applizierten Luftembolien hin.

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Impact of bubble size in a rat model of cerebral air microembolization

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Abstract

Background: Cerebral air microembolization (CAM) is a frequent side effect of diagnostic or therapeutic interventions. Besides reduction of the amount of bubbles, filter systems in the clinical setting may also lead to a dispersion of large gas bubbles and therefore to an increase of the gas–liquid-endothelium interface. We evaluated the production and application of different strictly defined bubble diameters in a rat model of CAM and assessed functional outcome and infarct volumes in relation to the bubble diameter.

Methods: Gas emboli of defined number and diameter were injected into the carotid artery of rats. Group I (n = 7) received 1800 air bubbles with a diameter of 45 μm, group II (n = 7) 40 bubbles of 160 μm, controls (n = 6) saline without gas bubbles; group I and II yielded the same total injection volume of air with 86 nl. Functional outcome was assessed at baseline, after 4 h and 24 h following cerebral MR imaging and infarct size calculation.

Results: Computer-aided evaluation of bubble diameters showed high constancy (group I: 45.83 μm ± 2.79; group II: 159 μm ± 1.26). Animals in group I and II suffered cerebral ischemia and clinical deterioration without significant difference. Infarct sizes did not differ significantly between the two groups ($p = 0.931$ *u*-test).

Conclusions: We present further development of a new method, which allows reliable and controlled CAM with different bubble diameters, producing neurological deficits due to unilateral cerebral damage. Our findings could not display a strong dependency of stroke frequency and severity on bubble diameter.

Keywords: Animal experimentation, Cerebral infarction, Cardiopulmonary bypass, Cardiac surgical procedures, Gas embolism

Background

Cerebral air microembolization (CAM) as an iatrogenic event represents a well-known complication of various invasive medical interventions. In the fields of open-heart surgery, neurosurgery, and diagnostic or therapeutic neuroradiology, CAM contributes to increased periprocedural morbidity and mortality, warranting the development of preventive strategies [1-3].

Severe CAM, i.e. large volume cerebral air embolization, is a rare condition that results in severe brain damage. According to clinical observations and animal studies, fatality caused by the infusion of large gas volumes seems to be undisputable [4,5]. To date, the consequences of CAM with small amounts of embolized air are still unknown. Frequently seen in cardiopulmonary bypass (CPB) assisted surgery or angiography, CAM can lead to persistent focal neurological and neuropsychological deficits, often without the display of manifest cerebral infarction on MRI [2,6]. Recent clinical trials suggest that the diminution of CAM can improve neuropsychological outcomes within the first three months post intervention [2]. Pathophysiological background, thresholds for emboli load, and other determinants of clinical outcome after embolization are largely unknown.

Mechanisms of CAM-induced tissue damage exceed mere mechanical consequences such as compression

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against the endothelial capillary wall and obstruction of blood flow by a lodging bubble [7]: Constituting a foreign substance, air bubbles provoke clotting activation [8-11], inflammatory response with neutrophil aggregation and complement activation [12,13] with the production of radical species leading, amongst others, to an increased vascular permeability and triggering a complex immunological and ischemic cascade of tissue injury. These pathomechanisms are initiated on the surface of the bubble with the gas–liquid-endothelium interface as a driving force [7].

The use of filter systems during CPB-assisted surgery can reduce the amount of gaseous cerebral emboli, but it seems conceivable that the mesh-like structure of these filters may also cause a dispersion of large gas bubbles into numerous smaller particles. This would substantially increase the total bubble surface and, therefore, intensify the potentially hazardous gas–liquid-endothelium contact in turn. Not least because of the absence of an appropriate animal model and the inability to control and monitor the diameter of the bubbles, knowledge of cerebral air embolism is sparse and little is known about the influence of bubble size [14].

Based on the hypothesis that bubble size has an impact on the neurological outcome and the occurrence of cerebral ischemia following CAM, we aimed to prove feasibility and reliability of production as well as application of gaseous bubbles with different defined bubble diameters by means of a recently developed custom-made bubble generator [15]. Furthermore, we evaluated embolization effects with regard to the functional neurological outcome, frequency and volume of cerebral ischemia in relation to bubble diameter.

Methods

Production and application of microbubbles

For the production and application of air microbubbles, we used a custom-made device, as previously established by our group [15]: the device consists of a customized glass capillary with a diameter of 15-40 μm, positioned in a larger glass tube with a diameter of 450 μm (Rincaps, Hirschmann Laborgeraete GmbH) and a slight taper on one side (Figure 1). The space between these two tubes was jetted with saline at a constant flow of 20 ml/h driven by an infusion pump (MC Medizintechnik GmbH, Alzenau). Simultaneously, air at a precisely adjustable pressure, controlled by a regulator (Watson Smith Ltd., Leeds, England), was piped through the inner capillary, requiring pressure from 0.5 to 1.5 bar to vary the number of produced bubbles.

The number and size of air bubbles were carefully adjusted at a constant rate before the device was connected to the carotid artery of the rat. During this process, a hydrostatic pressure was obtained within the system simulating the physiological mean arterial blood pressure of each animal under anesthesia. After adjustment, a glass valve between the Teflon tubing and the glass tube was opened and saline with air bubbles was allowed to flow into the carotid artery of the rat, joining the bloodstream.

Quantification of the number and size of air microbubbles

The bubble formation was recorded by a high-speed optical image capturing system (Camera A602f-2, Basler, Switzerland) focusing on the tapering (Figure 1) and connected to a personal computer (MacBook Pro, Mac OS X, version 10.5.1). A custom-made software allowed

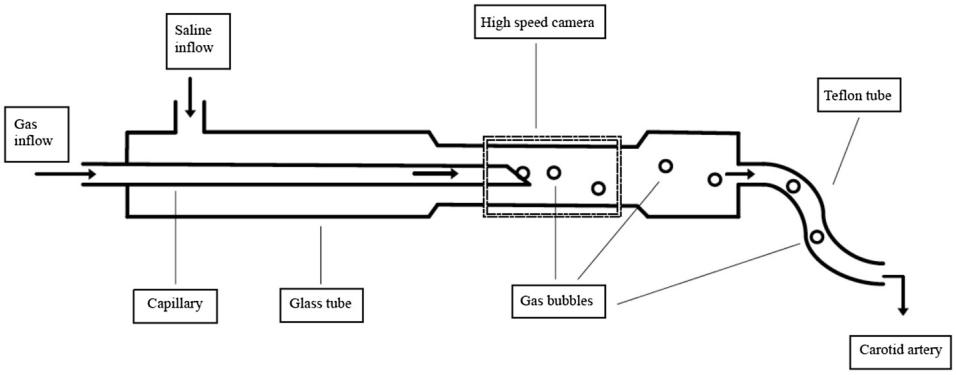

Figure 1 Schematic diagram of the custom-made bubble generator. Controlled alteration of air bubble number and size can be obtained by the variation of airflow, saline flow, diameter, and position of the capillary within the outer tube. Automatic recording and determination of bubble number and size is performed using a high-speed optical image capturing system connected to a computer with custom-made software.

real-time recording and analysis of the number and size of the air bubbles flowing into the carotid artery of the animal.

Animal preparation

All procedures were carried out in accordance with our institutional guidelines and the German animal protection legislation and were approved by the regional ethics committee (Regierungspraesidium Darmstadt; AZ B2/203). Twenty male Wistar Unilever rats (HsdCpb:WU; Harlan Winkelmann, Borchen, Germany) were anesthetized with 5% isoflurane in an enclosed chamber. During surgery, anesthesia was maintained with 2-3% isoflurane delivered in air at 0.5 l/min through a closely fitting facemask under sustained spontaneous breathing. Analgesia was achieved by subcutaneous injection of Carprofen 5 mg/kg (Rimadyl, Pfizer, Germany) 30 min prior to surgery. During these procedures, the body temperature of the rat was continuously monitored with a rectal probe and maintained at 36.5-37°C with a thermostatically controlled heating pad.

The right common carotid (CCA), internal carotid (ICA), and external carotid artery (ECA) were exposed by a midline incision of the neck. After isolation of the ECA, the superior thyroid and occipital arteries were cauterized. Then the distal portion of the ECA was ligated with a 5–0 suture and intersected to create an ECA stump with a length of approximately 5 mm. Furthermore, the pterygopalatine branch of the ICA was ligated with a 5–0 suture.

Application of air bubbles to cerebral circulation

The Teflon-50 tubing (Figure 1) was deaerated, connected with the air bubble generator, and then inserted into the ECA stump through an arteriotomy. To ensure the free movement of the air bubbles with the current of the physiological blood stream from the CCA to the ICA, the tip of the tubing was placed close to the carotid bifurcation under visual control. Unintended inlet of air was avoided by fixation of the tubing within the ECA stump through ligature and controlled optically via the surgical microscope during the whole injection procedure.

To minimize total injection volume, we chose the lowest infusion speed carrying the air bubbles appropriately: the infusion was performed within approximately 2 minutes at a speed of 20 ml/h, equivalent to an infusion volume of approximately 0.65 ml saline per animal. A PE-50-catheter was inserted into the tail artery from 30 minutes before until 30 minutes after carotid artery infusion in order to monitor the arterial blood pressure and obtain blood samples for arterial blood gas analysis. After air infusion, the ECA was ligated, the tubing removed, and the wounds closed carefully. Then the animals were allowed to recover from anesthesia.

Functional testing

Functional testing was performed by investigators blinded to group assignment at baseline, after 4 h, and after 24 h using a Neuroscore, as previously described by Nedelmann et al., and the Rotarod test: The Neuroscore assesses dimensions of motor, coordinative, and sensory function by testing contralateral forelimb flexion, hemianopia, sensory to left side touch, instability to lateral push from the right, and coordination when walking on the ground. For each item, up to 10 points can be allocated. The Neuroscore can range from 0 (no deficit) to 90 (very severe neurological deficit) [16].

During Rotarod testing, the wheel was continuously accelerated from 0 to 30 rpm within one minute. The maximum speed tolerated by the rats without falling off or spinning around was documented [17].

MR imaging

MR imaging was carried out 24 hours after intervention. Animals were fixed in a body restrainer with a tooth bar and a cone-shaped head holder and placed in an MRI tomograph (Bruker PharmaScan 7.0 T, 16 cm, Ettlingen, Germany), which operates at 300.51 MHz for ^{1}H-imaging and is equipped with a 300 mT/m self-shielding gradient system.

The respiratory rate (50-70/min) was monitored with a pressure probe placed between the restrainer and the animal's thorax. Anesthesia was maintained with isoflurane delivered in air at 0.5 L/min. The isoflurane concentration was varied between 2.0% and 3.0% to keep the respiratory rate between 35 and 45/min. The temperature was monitored using a rectal probe and maintained at 37°C by a thermostatically regulated water flow system throughout the imaging protocol.

A Carr-Purcell-Meiboom-Gill spin echo imaging sequence was used to map lesion and hemisphere volumes. Six contiguous coronal slices with a thickness of 2 mm (gap of 0 mm) were acquired (Field of view 37 × 37 mm, matrix 512 × 256, repetition time 3833.5 msec, 12 echoes: echo time 18–216 msec (Δ echo time 18 msec), acquisition time 16.25 minutes, number of excitations 1).

The T2-relaxation time was measured in regions of interest within the center of the ischemic area on all slices displaying ischemic lesions and a corresponding position on the contralateral hemisphere. The difference in T2RTs between the ischemic and unaffected hemispheres was calculated.

Computer aided planimetric assessment of ischemic lesion volumes and hemispheric volumes were performed by two blinded investigators experienced in experimental stroke MRI. The ipsilateral and contralateral hemispheric volume and lesion volume on T2WI were determined using the Image J 1.25 s image analysis software (National Institutes of Health, USA). The edges of the hemispheres

were traced manually on each slice using neuroanatomic landmarks. Hyperintense ischemic lesions were traced manually in a similar fashion. The areas were then summed and multiplied by the slice thickness to calculate volumes. Lesion volumes were calculated with and without edema correction and expressed as a percentage of the hemispheric volume as described previously [18]:

$$\%\mathrm{HLVuc} = \mathrm{LV}/((\mathrm{HVc} + \mathrm{HVi})/2) * 100)$$

$$\%\mathrm{HLVec} = (\mathrm{HVc2} + \mathrm{LV} * (\mathrm{HVc} + \mathrm{HVi}) - \mathrm{HVi2})/ (\mathrm{HVc} * (\mathrm{HVc} + \mathrm{HVi})) * 100$$

(%HLVuc = percent hemispheric lesion volume – not corrected for edema; %HLVec = percent hemispheric lesion volume – corrected for edema; HVc = volume of the contralateral hemisphere; HVi = volume of the ipsilateral hemisphere; LV = lesion volume)

Experimental protocol

Twenty rats (body weight 300-347 g) were randomized into 3 groups: the animals in group I (n = 7) received 1800 air bubbles with a low target diameter of 45 μm. Group II (n = 7) received 40 air bubbles with a higher target diameter of 160 μm, yielding equal total volume of administered air per rat of 86 nl in both groups. The animals in Group III (n = 6) served as sham-operated controls with the infusion of an identical volume of saline without application of air bubbles. Functional testing was performed at baseline, at 4 h, and at 24 h after intervention, followed by MRI examination.

Statistical analysis

The Kolmogorov–Smirnov Test was used to test for normal distribution of data; homogeneity of variance was tested by Levene-Test. Group differences were tested by non-parametric Kruskal-Wallis Test. Then the individual groups were subjected to subsequent post-hoc analysis with Mann-Witney-*U* Test. The p-value $p < 0.05$ was considered statistically significant. The data are presented as mean ± standard deviation.

Results

Four animals had to be excluded from analysis: one animal in group I received bubbles with a mean diameter much higher than the target size of 45 μm due to technical problems in adjusting the bubble size. During bubble injection of an animal in group II, flow problems occurred and bubbles conglomerated at the tip. Another rat in group II died 5 hours after the intervention. A fourth animal showed severe hemodynamic instability as well as apneas during saline application. The remaining sixteen animals (group I n = 6, group II n = 5, group III n = 5) survived and completed the study protocol.

Reliability of air bubble generation

For the present experiment, we selected two groups with target air bubble diameters of 45 and 160 μm compared to a sham-operated control group. The actual bubble sizes, as determined by the computer-aided camera system, were 45.83 μm ± 2.79 (range 42-49 μm) and 159 μm ± 1.26 (range 157-160 μm). The effective bubble count injected into the carotid artery averaged out at 1808.5 ± 11.04 in group I and 40.17 ± 0.41 in group II.

Functional outcomes

In the sham-infusion group, no pathological findings in Neuroscore performance were detectable. Animals in groups I and II showed clinical deterioration after bubble infusion as determined by the Neuroscore: In group I, the mean neurological score was 15 ± 11.83 after 4 h and 10 ± 5.47 after 24 h, and in group II, it was 19.17 ± 11.14 after 4 h and 19 ± 10.24 after 24 h. Compared to the control group (III), these findings appeared to be statistically significant. However, between the two bubble sizes of 45 and 160 μm, differences after 4 h ($p = 0.931$) and 24 h ($p = 0.177$) did not reach statistical significance.

In animals of all groups, the Rotarod performance worsened slightly after injection. At baseline, the mean maximum speed tolerated by the animals of group I was 23 ± 4.52 rpm; at 4 h and 24 h after intervention, test performance decreased to 21 ± 7.35 rpm for both time points. Animals in group II tolerated a mean speed of 22 ± 3.10 rpm at baseline ($p = 0.664$), 19 ± 11.01 rpm after 4 h ($p = 0.792$), and 20.4 ± 10.90 rpm after 24 h ($p = 0.931$). Between these two groups, no statistical significance could be detected.

Cerebral infarction on MRI

According to T2-weighted MR imaging after 24 h, no cerebral infarction could be detected in the control group (III). The infusion of air bubbles with a diameter of 45 μm (group I) and 160 μm (group II) resulted in ischemic infarction within the vascular territory supplied by the right internal carotid artery of four animals in each group (Figure 2 and 3). The assessment of infarct size showed a mean ischemic affected hemispheric volume of 5.18 ± 8.91% in group I and 2.48 ± 3.65% in group II, achieving no statistical significance ($p = 0.931$, Figure 3).

Discussion

CPB-assisted surgical interventions remain one of the most important causes of CAM; thus, filter systems have been suggested to reduce the number of bubbles. Common filters are installed in the arterial line of extracorporeal circulation, acting as a strainer by trapping bubbles that are larger than its pores [19,20]. However, besides increasing resistance to the flow itself, progressive filling with debris and fibrin, activation of coagulation cascade, and the

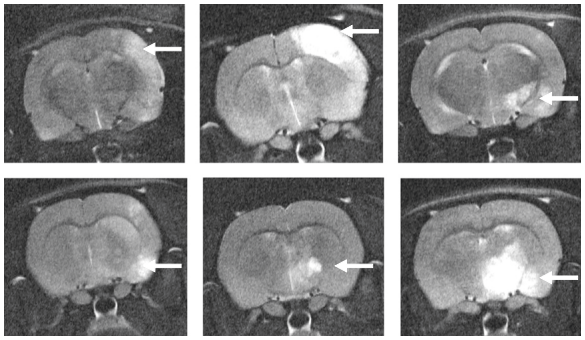

Figure 2 Cerebral MRI. Representative examples of T2-weighted MRI 24 h after embolization of small (1st row) or large (2nd row) bubbles. Note the arrows indicating cortical and subcortical ischemic lesions displayed in white.

complement and immune response [7], it is possible that the structure of these filters causes dispersion of larger bubbles into numerous smaller ones. In consequence, this would increase the gas–liquid-endothelial interface, which is known to be a significant factor of CAM-mediated tissue damage by activation of inflammatory response, the complement as well as the clotting system [7-13].

Hence, it is reasonable to proof whether bubble size has an impact on the neurological outcome or the occurrence of cerebral infarction and if markedly expanded regions of ischemia may reflect the extensive increase of the gas–liquid-endothelium contact interface in turn.

For decades, technical problems hampered standardized and reliable investigation of cerebral air embolism in basic research such as problems of selective arterial injection, disruption of physiological blood circulation, excessive volume of the air embolus, and varying bubble size [21]. Most of these problems could be solved, but bubble sizes remained difficult to control: Nearly all animal studies on cerebral air embolism have used the injection of different volumes of air as a bolus or repetitively and titrated to a certain extent of damage without the opportunity to display and verify bubbles and their size [14,22-26].

To investigate the impact of bubble size, we used our recently established rat model for air microembolism allowing the application of gaseous bubbles under preserved physiological cerebral blood flow [15]. In the past, investigations on CAM revealed a dose-dependent toxicity of air volume and functional parameters: Gerriets et al. (2010) used a bubble diameter of 160 μm with an

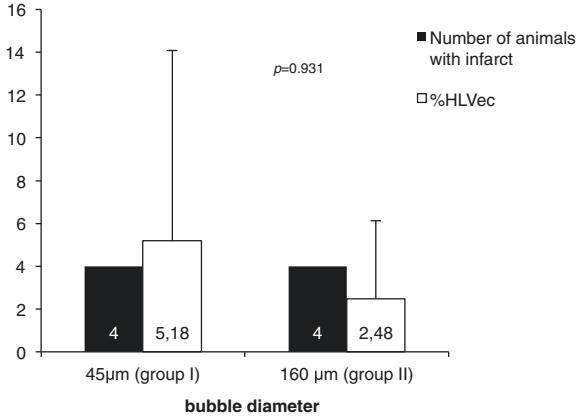

Figure 3 Number and size of cerebral infarction. Four animals in each group suffered cerebral infarction detectable on MRI. Infarct sizes, expressed as the edema-corrected hemispheric lesion volume differed not statistically significant (5.18 ± 8.91% vs. 2.48 ± 3.65%, $p = 0.931$ *u*-test).

increasing number of bubbles, showing worse clinical outcomes at higher gas emboli counts [15]. Jungwirth et al. (2007) revealed a dose-dependent relationship between CAM and survival, neurological outcome, and histological outcome [24]. The present study compares two different bubble sizes yielding the same total injection volume of 86 nl, which -according to findings from preliminary experiments- seems to represent a vulnerable threshold for the reproducible provocation of cerebral infarction in a rat brain [15]. Technically, the custom-made device we used is able to produce bubbles with a diameter of 40-250 μm. Herein, we chose 45 μm for small bubbles and 160 μm for the larger ones, representing two different sizes within the range that our device can produce [15]. With respect to the number and diameter of gaseous bubbles, we could demonstrate feasible and highly reliable production and injection of small 45 μm-bubbles with a low standard deviation.

We were able to show that functional performance according to the Neuroscore worsened significantly after embolization when compared to the sham-operated rats. The tendency to larger bubbles leading to a worse functional outcome has to be interpreted with caution, because scores showed broad standard deviations and differences did not reach statistical significance here, which may be attributed to the low number of animals used. In our experiment, air microembolism regularly caused cerebral ischemic infarction for both bubble sizes, though differences in frequency of ischemia between group I and II could not be verified. Due to the extensive increase of bubble surface with smaller bubbles and the suspected noxiousness of the gas–liquid-endothelium contact, we considered ischemic infarction to increase in a comparable order of magnitude. The size of ischemic lesions, as detected by the MRI scan, appeared to be almost doubled for small bubbles; though, differences in lesion volume between the two groups did not reach statistical significance. In summary, we could not find any significant differences between the two bubble sizes concerning functional outcome parameters, number of infarctions, or lesion volume, despite a 45-fold increase in the number of bubbles, i.e. a 4-fold increase of total bubble surface respectively, in the 45 μm group.

Besides statistical caveats due to a reduced statistical power, further pathophysiological considerations may explain the absence of distinct effects: It seems to be reasonable but not proven that bubbles of different size will get stuck analogously in vessels of different sizes [14]. According to a dynamic bubble behavior, bubbles may not maintain their size and split, aggregate or dissolve during downstreaming within short time. This may lead to a uniform bubble size within the terminal vascular bed, causing comparable probability of infarction, lesion volume, and consecutive functional decline. Furthermore, there is experimental evidence that even gas bubbles small enough to pass through arterioles and the capillaries without verifiably occluding the vessel can lead to neurological deficits [22,27,28]. This may be supported by an observation from the venous system of the lung, where leukocyte and platelet accumulation around gaseous bubbles was observed on flowing bubbles [29].

The discrepancy between functional deterioration and infarct volumes in the intervention groups, supplemented by the observation that one rat in each intervention group showed clinical deterioration without displaying cerebral infarction on MRI, question cerebral ischemia as the only pathological correlate of CAM-mediated tissue injury. Clinical studies have revealed that not every patient with cognitive decline after CPB-assisted surgical intervention shows morphological changes such as ischemic stroke detectable by MRI, supposing that the majority of cerebral damages that become clinically obvious post-intervention is still beyond the detection level of MRI [2,30-33]. Not least because of the large number of different existing animal models, determinants and cut-off points for morphological or cognitive damage due to subtle CAM as well as pathophysiological changes with “substructural” damage are yet undefined and need more experimental data [7,24]. Our animal model of CAM offers a strongly controlled setting that may help to define thresholds to reproduce clinical deterioration without overt morphological changes in future.

Eliminating bigger bubbles seems to be insufficient to prevent post-intervention deterioration, and this may explain why supplements of currently used filter systems such as the dynamic bubble trap (DBT) lead to better clinical outcomes. Importantly, the DBT eliminates rather than fragments gas bubbles. Hence, clinical trials have shown a reduction of microembolic signals and CAM-associated effects with filter systems or a combination of filters with a bubble trap that reduced the number of bubbles [2,34].

It remains debatable, if the small effect size would have required higher animal numbers per group to increase statistical power in the end. As well, limitations of our study may include the number of dropouts, further reducing the number of animals completing the study protocol. There are no data revealing homogeneity of bubble sizes in the clinical setting or the relation between harmful bubble sizes and air volume in humans and animals. Additionally, the animals studied here were healthy, in contrast to multimorbid patients normally undergoing CPB-assisted surgery. Beyond that, susceptibility differences of species to ischemia have to be taken into account when findings are compared.

There is no denying that even the best animal model cannot simulate a clinical situation in detail. To concentrate on the plain cerebral bubble effect, we rejected

interventions such as the heart-lung machine that may disturb the stability of vital signs by causing temperature changes or blood pressure dips, for example [24,35].

Conclusions

Present methodological evaluation revealed the feasibility of standardized and controlled CAM, producing neurological deficits due to unilateral cerebral damage with comparably low mortality. The device used can reliably produce and inject even small gaseous bubbles with a diameter of 45 μm. In the context of a small study group, our findings could not display a strong dependency of stroke frequency and severity on bubble diameter. A trend towards larger ischemic infarction with small bubbles and worse functional outcome with larger bubbles did not reach statistical significance.

Abbreviations

CAM: Cerebral air microembolization; CCA: Common carotid artery; CPB: Cardio-pulmonary-bypass; ECA: External carotid artery; %HLVec: Percent hemispheric lesion volume – corrected for edema; %HLVuc: Percent hemispheric lesion volume – not corrected for edema; HVc: Volume of the contralateral hemisphere; HVi: Volume of the ipsilateral hemisphere; ICA: Internal carotid artery; LV: Lesion volume; MRI: Magnetic resonance imaging; T2RT: T2-relaxion time; T2WI: T2-weighted imaging.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

All authors read and approved the final manuscript. All authors listed have made substantive intellectual contributions to the study and this manuscript: MJ and MY participated equally in conception, rational, and design of the study, contributed in functional testing and drafted the manuscript. NS performed surgical interventions/ animal preparation, participated in application of microbubbles and functional testing as well as MRI-Imaging. JB made substantial contributions to concept, coordination and design of the study, accounted for cardio-surgical expertise, participated in statistical analysis. MN participated substantially in establishment of methodology and helped to draft the manuscript. MT partook in development and establishment of methodology, participated in MRI-Imaging, image-/ data-analyses (planimetry; assessment of infarct number and lesion volume) and statistical analysis. GB contributed fundamentally in MRI-Imaging, image-/ data-analyses (planimetry; assessment of infarct number and lesion volume) and administered radiological expertise. MK provided neurological expertise, helped to draft the manuscript and revising it critically for important intellectual content. PU contributed considerably to development, design and maintainance of the bubble generator, production of consumable parts of the device (i.e. capillaries, tubings etc.…) and generation and application of microbubbles during experiment. MS participated in development of bubble generator, made substantial contributions to the concept and design of the study, accounted for cardio-surgical expertise and funding. TG participated in development of bubble generator and establishment of methodology, conceived the study, participated in conception and coordination of the study, assured funding and helped to draft the manuscript.

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4.3. Pseudohallucinations After Cardiac Surgery: Clinical Series (A3).[116]

Sabrina Kastaun, Sa-Ra Lie, Mesut Yeniguen, Markus Schoenburg, Tibo Gerriets, Martin Juenemann

Nach größeren Herzoperationen berichten Patienten häufig über sogenannte visuelle Pseudohalluzinationen, die sich weder mit einer deliranten Symptomatik noch einer psychiatrischen Grunderkrankung in Verbindung bringen lassen. Obwohl sich die Patienten von diesen Trugbildern distanzieren können, werden sie oft als beunruhigend empfunden und führen auf Seiten des behandelnden Arztes zu Unsicherheiten bezüglich ihrer Behandlungsindikation sowie der Therapieoptionen. Ätiologie und Inzidenz dieses Phänomens sind bis dato unbekannt.

In dem ersten Teil dieser klinischen Fallserie wurden exemplarisch Beschwerden und der klinische Verlauf dreier nicht-deliranter Patienten mit transienten visuellen Halluzinationen nach Herzoperationen mit kardiopulmonalem Bypass beschrieben.
Zur Abschätzung der Inzidenz dieser postoperativen Halluzinationen untersuchten wir in einem zweiten Teil 100 Patienten 48 ± 12 Stunden nach einer Operation mit extrakorporaler Zirkulation anhand eines kurzen Screeningfragebogens. Patienten, die über visuelle Halluzinationen berichteten, erhielten zwischen dem 4. und 9. Tag nach der Operation eine neurologische und psychiatrische Untersuchung, eine ophthalmologische Untersuchung mit Gesichtsfeld- und Sehschärfenbestimmung, eine neuropsychologische Beurteilung (Mini Mental Status Test, Confusion Assessment Method) und - wenn möglich - eine kraniale MRT.

Wir identifizierten 11 nicht-delirante Patienten (3 weiblich, 8 männlich; 64,8 ± 12,3y) mit optischen Halluzinationen nach Koronararterien-Bypass-Operationen oder Aortenklappenersatz. Die Patienten beschrieben lebendige, typischerweise farbige Bilder von belebten oder unbelebten Objekten (d.h. Maschen, Personen, Farbspritzer). Die Halluzinationen wurden erstmals einige Tage nach der Operation beobachtet, traten typischerweise mehrmals pro Tag auf und dauerten von einigen Sekunden bis zu Stunden. Häufigkeit, Dauer und Intensität nahmen mit der Zeit ab und verschwanden innerhalb von 3 Tagen bis 3 Wochen. Das Phänomen trat nicht in Bezug zu Tageszeit, Aktivität oder Raumbeleuchtung auf. Die Patienten waren sich zu jeder Zeit der Unwirklichkeit dieser Wahrnehmungen bewusst. Kein Patient zeigte weitere psychiatrische oder neurologische Symptome oder litt an einer Migräne oder einer schweren Sehbehinderung. Eine MRT wurde bei 5/11 Patienten durchgeführt. Ein Patient wies mehrere kleine Infarkte im Bereich der mittleren und hinteren Hirnarterie auf.

Visuelle Halluzinationen treten häufig nach Herzoperationen auf und scheinen nicht mit einem postoperativen Delirium oder einer strukturellen Hirnschädigung in Zusammenhang zu stehen. Behandelnde Ärzte sollten die Benignität dieser Symptomatik klar kommunizieren und die Indikation einer Behandlung mit Sedativa oder Neuroleptika nur sehr streng und gegebenenfalls im Rahmen einer interdisziplinären Falldiskussion stellen. Weitere systematische, prospektive Studien sind erforderlich, um die genaue Inzidenz sowie die zugrunde liegende Pathophysiologie zu untersuchen.

Pseudohallucinations After Cardiac Surgery: Clinical Series

Sabrina Kastaun, Dipl Psych,*† Sa-Ra Lie, MD,*‡ Mesut Yeniguen, MD,*§ Markus Schoenburg, MD,†* Tibo Gerriets, MD,*§¶ and Martin Juenemann, MD*§

PATIENTS FREQUENTLY COMPLAIN about visual hallucinations after major cardiac surgery.[1] In some cases, the hallucinations are not related to postoperative delirium and the patients clearly are aware of the unreality of this sensory experience. To distinguish the latter from classic hallucinations, the term "pseudohallucination"—although often questioned—has been used in the classification of nonpsychotic perceptual disorders.[2,3]

Although potentially causing loss of confidence and uncertainty with the patient, therefore interfering with acute treatment and convalescence, the literature on this symptomatology related to cardiac surgery is sparse. Eriksson et al reported a considerably high rate of "hallucinations or illusions" occurring in patients with and without postoperative delirium after bypass surgery.[1] Unfortunately, the natures of these visual phenomena were not described in detail.

Herein, detailed descriptions are provided of 3 nondelirious patients presenting with nonpsychiatric, transient visual hallucinations several days after a cardiac surgery that included cardiopulmonary bypass. Furthermore, to estimate the incidence of this phenomenon, 100 consecutive patients were examined 48 ± 12 hours after cardiac surgery using a short screening questionnaire that addressed any changes in their visual perception. Patients who declared such symptoms had to answer semistructured questions related to the onset, nature, circumstances, and duration of these sensations, as well as to their feelings and ideas about them. A diagnosis of a delirium was an exclusion criterion. Subsequently, patients who reported pseudohallucinations received neurologic and psychiatric testing, ophthalmologic screening, neuropsychologic assessment (Mini Mental Status Examination,[4] Confusion Assessment Method,[5] and, if possible, cranial magnetic resonance imaging (MRI) between days 4 and 9 after surgery and were interviewed repeatedly until the phenomenon concluded.

CLINICAL SERIES

A 71-year-old man with a history of arterial hypertension, hypercholesterolemia, and permanent atrial fibrillation, as well as intense mitral valve insufficiency, tricuspid valve insufficiency, and 1-vessel coronary artery disease (CAD), underwent elective coronary artery bypass grafting (CABG), mitral valve annuloplasty, tricuspid valve reconstruction, and cryoablation for atrial fibrillation (total surgery time, 347 minutes; cardiopulmonary bypass (CPB) time, 164 minutes). Long-term medication included phenprocoumon, which was superseded perioperatively by heparin, bisoprolol, ramipril, amlodipine, torasemide, simvastatin, and hydrochlorothiazide. Beginning the first day after surgery, the patient perceived vivid, colored images of animals (eg, rats or giraffes) and inanimate objects (ie, colored cobwebs) appearing on the surfaces of walls and furniture, or even hovering in his room. The images mostly moved vertically. The symptoms disappeared 3 weeks after surgery.

A 69-year-old woman with a history of severe mitral valve insufficiency, aortic valve insufficiency, and 2-vessel CAD underwent elective CABG, mitral and aortic valve replacement, and subvalvular myectomy (total surgery time, 360 minutes; CPB time, 187 minutes). The patient's medical history revealed arterial hypertension, hyperlipoproteinemia, hyperuricemia, and chronic renal failure, which were treated medically with phenprocoumon, bisoprolol, ramipril, amlodipine, torasemide, simvastatin, acetylsalicylic acid, xipamide, and allopurinol. The patient first noticed pseudohallucinations on the third day after surgery. Animals resembling deer or moose appeared on walls and then dissolved laterally before they disappeared completely. In contrast to the previous case, the illusions resembled monochrome pencil drawings. Furthermore, the patient described problems with reading—letters appeared to be vertically split and glided sideways out of the book. The illusions stopped 18 days after surgery.

After elective cardiac surgery with mitral valve replacement (total surgery time, 244 minutes; CPB time, 123 minutes) because of a history of mitral valve insufficiency and 3-vessel CAD with CABG in 1996, an 81-year-old woman complained about pseudohallucinations. Her pre-existing conditions, including arterial hypertension, chronic obstructive pulmonary disease, and chronic renal failure, required medical treatment with spironolactone, torasemide, xipamide, acetylsalicylic acid, clopidogrel, nebivolol, simvastatin, amlodipine tiotropium bromide, and salmeterol. Twenty-four hours after surgery, she described brown grids appearing and moving across the

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faces of people in her room (eg, on nurses). Furthermore, the patient gave a vivid description of her treating nurse wearing strange glasses formed by multiple, small, multicolored squares (in a mosaic). The nurse was neither present at that time nor was she wearing colored glasses. Comparable to patient 2, patient 3 described problems reading, as the letters appeared to be vertically stretched and glided sideways out of the book. The phenomenon concluded 10 days after surgery.

Each patient received standard intravenous narcotic anesthetics, including sufentanil, propofol, and cisatracurium. Postoperative pain was treated with paracetamol and piritramide.

All 3 patients reported that the complex pseudohallucinations appeared several times per day, lasted up to 2 hours in the beginning, and were present continuously over the periods mentioned for each patient. However, the frequency and duration of the illusions then decreased over time; peri-ictal features were absent. The occurrences of the visual phenomena were not related to the time of day, the patients' activity, or the room lighting, and additional sensory phenomena such as auditory or olfactory phenomena were negated. All patients affirmed that the images only occurred while their eyes were open; in all of the cases, their hallucinations could be abolished by closing their eyes. All of the patients clearly could distance themselves from the hallucinations; that is, they had full insight into the unreal nature of the visual phenomena and were not frightened, except for some mild concerns about suffering from psychiatric or ocular disorders. None of the patients exceeded the cut-off ≤ 27 in Mini Mental Status Examination,[4] showed an acute change or fluctuated course in mental status, inattention, or indications for disorganized thinking, or altered level of consciousness, which are required for a diagnosis of delirium.[5]

In all of the cases, cranial MRI displayed age-appropriate, mild-to-moderate leukoencephalopathy without any indication of a cerebrospinal fluid circulatory dysfunction, intracranial hemorrhage, ischemic infarction, or inflammatory or space-occupying processes.

Neurologic and neuropsychiatric examinations revealed no focal deficits (ie, normal alertness, mental status, orientation, and memory function, with no pathologic findings concerning language, cranial nerves, motor [strength, tone, deep tendon reflexes] and sensory function, or coordination) as well as the absence of pyramidal/corticospinal signs. None of these patients had any history of migraine, epilepsy, or cerebrovascular diseases, or fulfilled the diagnostic criteria for a psychiatric disorder, and none of the examinations showed any signs of a cognitive or movement disorder, such as dementia or Parkinsonism. Ophthalmologic examinations indicated that all of the patients had normal or only mildly impaired vision appropriate to their ages, with visual acuity of at least 1.2 and completely unobtrusive investigation of the visual field.

The examination of 100 patients with a screening questionnaire identified 11 nondelirious patients (3 female, 8 male; 64.8 ± 12.3 y) with pseudohallucinations after CABG ($n = 4$) or aortic valve replacement ($n = 7$). Comparable to the aforementioned cases, the patients described vivid, typically colored images of animate or inanimate objects (eg, meshes, posies, individuals, and paint splatters). The pseudohallucinations were noticed first several days after surgery; their frequency, duration, and brightness decreased over time and disappeared within 3 days to 3 weeks. None of the patients had histories of severe visual impairment or suffered from migraines. Neurologic and neuropsychologic examinations found no evidence of any psychiatric or neurologic disorders. MRIs were performed in 5 of the 11 patients. One patient showed multiple small infarcts within the middle and posterior cerebral artery territory.

DISCUSSION

Three nondelirious patients presenting with pseudohallucinations for 10 to 21 days after major cardiac surgery are reported here. All of the cases were identified by the consulting neurologist within 4 weeks, suggesting that this phenomenon might not be uncommon. Nevertheless, information on the incidence of this phenomenon in patients who have undergone major cardiac surgery is sparse. Within the survey at the authors' hospital, 100 nondelirious patients were interviewed after major cardiac surgery, including cardiopulmonary bypass, with a short screening questionnaire on hallucinations. Eleven patients with pseudohallucinations after CABG or aortic valve replacement were identified, and each patient clearly was aware of the unreal nature of the sensations; neurologic, neuropsychologic, psychiatric, and ophthalmologic examinations found no relevant pathology. On MRI, only 1 patient showed multiple small, embolic cerebral infarctions, including in the right posterior territory.

Eriksson et al aimed to evaluate symptoms of delirium after CABG surgery. Delirium was diagnosed in 12 of 52 patients enrolled in the Eriksson et al study, and, compared with the present observations, a remarkably higher rate (50%) of nondelirious patients with "hallucinations or illusions" after CABG was reported. However, detailed information on the configuration, frequency, duration, and patients' distancing was lacking.[1] Further information on this phenomenon can be derived from several case reports: Eissa et al reported on a patient with visual hallucinations during the first 3 days after elective CABG,[6] and Laloux and Osseman published a case of postoperative hallucinations on the second day after carotid endarterectomy and CABG.[7] However, both patients only complained about hallucinations when their eyes were closed; in both cases, reports on MRI data were missing.

With respect to possible differential diagnoses for the present case series, migrainous or epileptic etiologies were considered unlikely because of the accordant personal and family histories, low stereotypy, and the fragmentation of imagery, missing headache, and peri-ictal features. The differential diagnosis of visual hallucinations includes peduncular hallucinosis (PH), which leads to complex pseudohallucinations that seem very similar to those occurring in the present patients but are associated with structural lesions of the midbrain and/or thalamus.[8] Most people with PH exhibit abnormal sleep patterns, with periods of wakefulness at night and abnormal daytime sleepiness. Furthermore, the visual symptoms show a diurnal pattern, with hallucinations mainly occurring in the evening hours and often including additional tactile or auditory perceptions.[9] Oculomotor disturbances, impaired arousal, dysarthria, and ataxia frequently are related to PH.[10]

Although all of the present patients experienced visual illusions comparable to PH, none of the presenting patients exhibited comparable sleep patterns, impaired arousal, or verifiable focal neurologic deficits, and MRI (including diffusion-weighted imaging) showed no overt structural lesions of the midbrain or thalamus. PH after cardiac interventions has been reported once in the literature: Kamalakannan et al[11] described an 84-year-old man with coronary artery disease. Twelve hours after cardiac catheterization, including angioplasty and stenting, he suffered from visual pseudohallucinations. Computed tomography revealed a lacunar infarct involving the midbrain. The pseudohallucinations disappeared 8 days postoperatively.

Pseudohallucinations also have been described in elderly patients with severely impaired vision, ie, due to macular degeneration, retinopathy, or corneal disease (Charles Bonnet syndrome). This syndrome can be characterized by vivid, elaborate, and recurrent visual pseudohallucinations in psychologically normal patients who have a full understanding of the unreal nature of the phenomenon. As in the present patients, the symptoms are restricted to the visual modality.[12,13] However, aside from ocular causes of impaired vision, lesions at any point within the central visual pathway can forward such a "release phenomenon," as a result of the deafferentation of visual input in the extrastriatal visual association cortex.[2,9,14,15]

As documented by the ophthalmologic examinations, all of the patients in the present report had normal or only mildly impaired vision (appropriate to their age), no overt lesions within the visual pathway on MRI, and a short duration of symptoms (2-4 weeks). The present cases, therefore, might represent a separate disease entity.

Cardiopulmonary bypass is associated with an increased risk for cerebral microembolization. The bypass time in the present case series ranged from 123 to 187 minutes. The incidence of cerebral microembolization seemed to depend on the duration of the CPB with the highest risk being during clamp manipulation, the release of clamps, and the filling of the empty, beating heart.[16,17] Gaseous microemboli emerge from the oxygenator or from the opened heart, and vessel manipulation can lead to the fragmentation of atherosclerotic plaque and, thus, to the release of particulate emboli. Cerebral microembolization can contribute to focal cerebral ischemia (with and without structural deficits on MRI) and to neuropsychologic decline.[18–20] It seems conceivable that pseudohallucinations after cardiac surgery might be the consequence of microembolic damage to the central visual pathway, because studies combining whole-brain, single-photon emission computed tomography and transcranial Doppler ultrasound after CABG surgery could show preferential emboli deposition in the occipital cortex.[21] This damage may provoke a "release phenomenon" that possibly may be below the detection limit of conventional MRI, with visual hallucinations as the clinical correlate of electrophysiologic hyperexcitability during the cortical recovery process.[22] Furthermore, studies with a multiaxial centrifuge showed transient sight disorders, such as hallucinations in connection with impaired cerebral tissue oxygenation,[23,24] which is a well-known condition during and early after CABG surgery.[25,26]

Several case reports describe different types of hallucinations after surgery in relation to anesthetics and analgesics, which also had been administered in the present patients.[27–29] However, most of these pharmaceuticals are part of standard care for major cardiac surgery, and causal attributions cannot be drawn from these data by implication. In the present small survey, pseudohallucinations were not related to postoperative delirium, but larger systematic studies are needed to exclude a relationship entirely and elucidate a potential role for the pre-existing disorders, drug therapy, and demographic variables in this phenomenon.

With respect to potential clinical, economic, and quality-of-life consequences, treating physicians should clarify the benignity of visual hallucinations after cardiac surgery that are not associated with delirium or overt structural brain damage. Patients may be treated incorrectly as delirious with neuroleptics and sedatives that, besides other adverse effects, potentially can increase the risk of further cardiovascular and cerebrovascular complications. If such hallucinations are mistaken and mistreated as a psychiatric/neurologic illness, unjustified costs can arise from medicamentous and nonmedicamentous supportive (psychologic) treatment, prolonged in-patient stay, and follow-up outpatient treatment. From the patient's point of view, this phenomenon can lead to uncertainty through stigmatization by a mental illness, potentially having an unfavorable effect on the patient's quality of life and recovery process.

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4.4. Continuous electroencephalography in a mixed non-neurosurgical intensive care population, an observational study (A4).[117]

Patrick Schramm, Judyta Luczak, Kristin Engelhard, Jasmin El Shazly, Martin Juenemann, Marlene Tschernatsch

Die kontinuierliche Elektroenzephalographie (continous electroencephalography, cEEG) verbessert die Überwachung des Gehirns bei bewusstlosen Patienten, die praktische Umsetzung auf einer Intensivstation ist jedoch oft schwierig. Die vorliegende Untersuchung führte die cEEG auf einer anästhesiologischen Intensivstation ein und diskutierte erste Erfahrungen.

Bewertet wurden hierzu im Einzelnen die Durchführbarkeit der cEEG, die auswertbare cEEG-Zeit, die Aussagekraft der automatischen Anfallserkennung, die vorherrschende Hintergrund-EEG-Aktivität, die Inzidenz epileptischer Anfälle und des Delirs sowie die Mortalität.

53 cEEGs von 50 Patienten mit einer im Median interpretierbaren Länge von 24 Stunden [IQR 20 bis 42 Stunden] wurden aufgezeichnet. Ein Patient erlitt einen Status epilepticus, während 5 Patienten nicht-konvulsive epileptische Anfälle boten. Die automatische Anfallserkennung detektierte den Status epilepticus sowie 3 von 10 nicht-konvulsiven Anfällen korrekt; es wurden jedoch ebenfalls 42 falsch-positive Anfälle diagnostiziert. Die vorherrschende Hintergrund-EEG-Aktivität waren alpha (9%), theta (17%), delta (26%) sowie burst-suppression (17%); in 30% der Fälle fand sich eine unterdrückte Hintergrundaktivität. Die EEG-Aktivität korrelierte weder mit der Eindosierung von Analgo-Sedativa noch mit der Inzidenz eines Delirs oder der Mortalität.

Die Durchführung einer cEEG über einen Zeitraum von 24 Stunden bei bewusstlosen Patienten auf einer anästhesiologischen Intensivstation ist nach einer entsprechenden Ausbildung in einem EEG-Labor und Einweisung des Pflegepersonals möglich. Die Verarbeitung der cEEG-Ableitungen durch die verwendete automatisierte Erkennungssoftware generierte falsch-negative/-positive Ergebnisse und konnte nicht die Analyse durch einen ausgebildeten Spezialisten ersetzen. Sie stellt gegebenenfalls jedoch eine Möglichkeit dar, das Bewusstsein für pathologische EEG-Muster zu schärfen. Eine direkte oder indirekte (Telekonsultation) Zusammenarbeit zwischen Intensivmedizin- und EEG-Spezialisten ist empfehlenswert, um die zielführende und sichere Anwendung der cEEG auf einer anästhesiologischen Intensivstation zu gewährleisten. Darüber hinaus erscheint die vorherrschende Hintergrund-EEG-Aktivität kein zuverlässiger Prädiktor des klinischen Ergebnisses zu sein.

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Continuous electroencephalography in a mixed non-neurological intensive care population, an observational study☆,☆☆,★

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ABSTRACT

Purpose: Continuous electroencephalography (cEEG) improves monitoring of the brain in unconscious patients, but implementation at ICU is difficult. The present investigation shows a way to introduce cEEG at an anesthesiological ICU and discusses the first experiences.
Materials and methods: The study analyzed the feasibility of cEEG, assessed the interpretable cEEG time, importance of automatic seizure detection, the incidence of seizures, the predominant background EEG activity, incidence of delirium and mortality.
Results: Fifty-three cEEGs of 50 patients with a median interpretable length of 24 hours [IQR 20 to 42 hours] were recorded. One patient had status epilepticus, while 5 patients had non-convulsive seizures. Automated seizure detection recognized the status epilepticus and 3 of 10 non-convulsive seizures, however, detected 42 false positive seizures. Predominant background EEG activity was alpha (9%), theta (17%), delta (26%), burst-suppression (17%), and suppressed background activity (30%). EEG activity correlated neither with dosage of analgo-sedative drugs nor with incidence of delirium or mortality.
Conclusion: Continuous electroencephalography recording is feasible and manageable. Automatic seizure detection was often false negative/positive; therefore, the interpretation of the cEEG should be supported by EEG-trained neurologists. Background EEG activity was not associated with outcome parameters, which suggests that background activity is a poor outcome predictor.

1. Introduction

Critically ill patients at the intensive care unit (ICU) often are unconscious due to either sedative drugs or to primary or secondary brain damage. Monitoring the brain function in these patients is difficult, however, with electroencephalography (EEG) the electrical activity of the brain can be recorded and this technology is increasingly used for the brain-monitoring of critical ill patients [1]. Especially continuous EEG (cEEG) monitoring over a longer period of time gives information about the background EEG activity and pathological pattern like seizures [2]. Seizures in critically ill patients often occur non-convulsive and can only be detected by EEG. To identify patients with non-convulsive seizures (NCS) and other pathological EEG pattern the European Society of Intensive Care Medicine (ESICM) and the European Resuscitation Council (ERC) recommend cEEG monitoring in unconscious patients [3,4].

These recommendations are difficult to implement at an anesthesiological ICU without continuous neurological support. A potential solution might offer the use of a cEEG combined with an automatic interpretation of the EEG. The present report therefore focuses on the feasibility to perform cEEG by trained non-neurologists and assesses the quality of the automatic analyses of cEEG of the first 50 patients.

2. Materials and methods

Monitoring unconscious patients with cEEG as clinical routine at the anesthesiological ICU at the University Medical Centre Mainz started,

Abbreviations: EEG, electroencephalography; cEEG, continuous electroencephalography; ESICM, European Society of Intensive Care Medicine; ICU, intensive care unit; IQR, interquartile range; NCS, non-convulsive seizures; SD, standard deviation.

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after a test period of 3 months, in April 2014. Collecting the raw cEEG data for scientific interpretation was approved by the local ethics committee. cEEG was measured in adult ICU unconscious patients receiving low dosages or no sedative drugs. None of the patients had a history of epilepsy. cEEG recording was performed after first treatment and stabilization of the patients without assumable need for transportation and without/after acute shock. cEEG was recorded as long as an interpretable EEG signal could be detected or until more than 3 of 10 electrodes became dysfunctional. All cEEGs recorded during the first year after implementation of the cEEG recording were analyzed and the results were discussed in the present report.

Electroencephalography registration was learned at two experienced EEG laboratories at the University Hospital of the Justus Liebig-University, department of neurology (Giessen, Germany) and at the University Medical Centre Mainz of the Johannes Gutenberg-University, department of neurology (Mainz, Germany) by PS. A nurse and medical student (JL) were further instructed in EEG registration by PS. The nursing team of the ICU was trained in handling the monitored patients in regard of careful head movements and handling the additional cables.

Electroencephalography was recorded using the EEG-1100-system (NIHON KOHDEN Europe GmbH, Rosbach, Germany). Ten EEG silver cup electrodes were placed according to the 10–20-System (Fp1, F3, C3, P3, T3, Fp2, F4, C4, P4, T4) and fixed with Genuin Grass® EC2® (Natus Neurology Europe, Langenfeld, Germany) electrode paste after carefully abrasion of the skin.

cEEG recordings were analyzed afterwards by blinded, EEG trained investigators, one of them a board certified EEG physician (MT). cEEG analysis focused firstly on the quality of the data and time of interpretable recordings, followed by analysis on predominant background EEG activity, artifacts, rhythmic pattern, and epileptic discharges. Furthermore, the raw cEEG was automatically Fourier transformed and visualized as density spectral array (Neurofax®, version 06–93, NIHON KOHDEN) and automatically analyzed for seizure activity (Persyst ICU Continuous Monitoring, Version 12, Persyst Development Corporation, California, USA).

The main objective of the present report was the feasibility of cEEG monitor at an anesthesiological ICU for a relevant time of 24 hours or more without special technical or neurological support. Furthermore, the correctness and usefulness of automatic seizure detection software compare to the findings of the EEG trained physicians was investigated. Secondarily, the predominant background EEG activity and the incidence of seizure activity, diagnosed by the EEG trained investigators, in relation to delirium and ICU mortality in this unconscious ICU population was described.

2.1. Statistical analysis

Physiological data are expressed as mean and SD for normally distributed values or median and inter quartile range [IQR]. Predominant background EEG activity was transferred in an ordinal matter with an assumable lower brain activity ranging from alpha- (group 1), theta- (group 2), to delta-activity (group 3) followed by burst-suppression-activity (group 4) and suppressed background activity (group 5). Pure ordinal data were compared using Mann–Whitney-U-Test and comparison ordinal data with continuous data a Spearman's rho test were calculated (MATLAB R2016a, MathWorks Inc, Natick, MA).

3. Results

Fifty-three cEEGs were measured in 50 unconscious and mechanically ventilated patients at the ICU. Forty patients received analgesia with sufentanil and 27 additionally received propofol. Thirty-three patients' needed the vasopressor norepinephrine in a low to moderate dosage. Twelve patients received elective surgery, 24 patients received emergency surgery and 15 patients had a medical emergency. The median duration of ICU stay was 27 days [13 to 59 days]. During stay at the ICU 19 patients suffered a delirium detected by the CAM-ICU test, 6 of them died. Additionally, 13 patients without delirium died. (for detailed patients' data see Table 1.)

The cEEG measurement started in median at day 5 [2 to 10 days] after ICU arrival. The median duration of cEEG measurement was 28 hours [22 to 45 hours]. After a median of 24 hours [20 to 42 hours] the cEEG was no more interpretable due to high impedance, dispatched electrodes and, therefore, too much artifact. In total 1627 hours of cEEG with 1458 interpretably hours were recorded during this investigation.

Six of the patients (12%) showed seizure activity, 5 of them without clinical signs of convulsions were diagnosed as NCS. One of the patients had treatment refractory generalized status epilepticus and died at the ICU. The remaining 5 patients showed secondary generalized self-limiting seizure activity (one NCS episode in 3, 2 NCS episodes in one and 5 NCS episodes in one of the patients), none of them died, one suffered from delirium. These patients were all treated with sufentanil and propofol. Mean age, kind of surgery or medical illness, incidence of delirium, ICU mortality and the length of stay at the ICU of the patients with NCS did not differ compared to the whole study population.

The automatic seizure detection showed seizure activity in the status epilepticus patient with very good accordance. Regarding the 5 patients with self-limiting NCS, 3 of the 10 NCS episodes were detected by the software. In 38 of the 53 recorded cEEGs, seizure detection software correctly displayed no seizure activity. In the remaining 15 cEEGs 42 false-positive seizures were displayed during a good EEG quality and further 60 false-positive seizure displayed while EEG quality was poor.

The predominant background EEG activity in the individual cEEG recordings was alpha in 9%, theta in 17%, delta in 26% of the patients; in 17% predominant background EEG activity was burst-suppression and in 30% of the cEEG recordings completely suppressed EEG activity could be detected (amplitude <5 μV). No correlation can be found between predominant background EEG activity and dosage of analgosedative drugs (propofol: $rho = 0.027$, $P = .89$ and sufentanil: $rho = 0.325$, $P = .05$). Furthermore, neither mortality ($P = .18$) nor incidence of delirium ($P = .67$) nor duration of ICU stay ($P = .9$) correlated with predominant background EEG activity (Fig. 1).

4. Discussion

The present study included 50 patients at a non-neuro specialized ICU who remained unexpected unconscious after deep sedation was terminated although no pre-existing neurological disorders have been diagnosed. In these patients the cEEG recordings, performed by anesthesiologists and nurses, was feasible and of good quality with interpretable measurements over 24 hours. Automatic seizure detection software showed too many false positive and false negative hits and can, therefore, not replace EEG trained physicians. Interestingly, in the observed population neither suppressed main EEG background activity nor NCS were predictors for poor outcome.

Table 1
Physiological data and outcome parameters.

Age [years]	63 ± 19
Gender masculine/feminine [n]	35/15
Sufentanil [n]	40
Dosage [μg/h]	10 [0–20]
Propofol [n]	27
Dosage [mg/h]	80 [0–140]
Norepinephrine [n]	33
Dosage [μg/h]	500 [0–1400]
Stay at ICU [days]	27 [13–59]
ICU-mortality [n]	19
Delirium incidence [n]	19

Number of patients in the observed population was presented as count (n). Parameters are expressed as mean ± SD or median and inter quartile range [IQR].

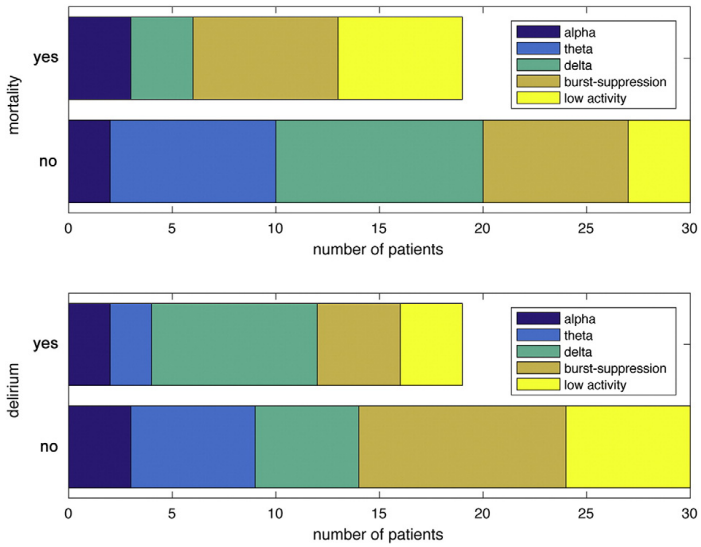

Fig. 1. Relationship between the predominant background EEG activity and the mortality/delirium incidence. The figure represents the number of patients with predominant background EEG activity of alpha (dark blue), theta (blue), delta (green), burst-suppression (brown) or suppressed (yellow) in the relationship of mortality (upper graph) and incidence of delirium (lower graph). In the upper graph patients who died at the ICU are shown in the upper bar (yes) and patients who survived, in the lower bar (no). In the graph below, the number of patients suffering from delirium is shown in the upper bar (yes), and the number of patients without delirium is shown in the lower bar (no).

In the present report the technical feasibility to record cEEG by a trained physician and nursing personal with a good signal-quality during the recommended 24 hours was proved. However, the analysis of the raw signal during the recording by non-EEG-trained ICU physician was not reliable. Therefore, the present data support the recommendation that a board certified neurologist, with further special experience in cEEG of unconscious critically ill patients, analyze the cEEG [5]. As according to the present data the recording of cEEG does not require an EEG specialist, it is also possible that alternatively a network of experts using tele-consultation, as implemented for example in parts of USA and France, will be sufficient to shorten the time of analysis while maintaining the high quality of the interpretation [6,7]. The technical feasibility to measure cEEG by ICU physicians and nurses, as shown in the present observation, in combination with a teleconsultant neurological service will spread the use of cEEG and meet the increasing demand for cEEG.

The analysis of raw cEEG is time-consuming and needs specialists to interpret the findings correctly. It is postulated that automatic procession of the raw EEG helps to detect changes of the background activity and occurrence of pathological pattern, which then can be further analyzed by an EEG-specialist [5]. This postulation was supported by the observation that nurses and non-neurophysiologists may detect NCS typical changes in the processed cEEG [8]. The present observation shows, that in many of the patients the automatic seizure detection software correctly indicated no seizure activity. But a relevant rate of false positive (42) and false-negative (7) results were also found. Sixty false-positive detections were due to poor cEEG quality which can be easily clarified even by non-specialists. Nevertheless, at the present time the used automatic seizure detection cannot replace the EEG-specialist, but, in combination with a processed EEG, automatic seizure detection will more easily identify patients and EEG-patterns which lead to reasonable consultation of the specialist.

cEEG recording in patients with unexpected unconsciousness without primary brain diseases is recommended to detect NCS which may occur in 8% to 10% of these patients [3,9]. In the present report seizures occurred in 12% of the patients ($n = 6$), which was in accordance to the aforementioned studies [10,11]. One of these patients had status epilepticus and died; the remaining 5 patients had self-limiting NCS and survived. The relevance of such self-limiting NCS detected with the cEEG on the outcome of the patients is still unclear. Three of 101 patients after cardiac surgery suffered from NCS with good neurological outcome [12]. Similar findings are reported by an investigation in 98 patients with severe sepsis; 11 of these patients suffered NCS but had good clinical outcome [13]. In contrast, a retrospective study of surgical ICU patients showed NCS in 24 of 154 patients and NCS was identified as an independent predictor of poor outcome [14]. Because of the low incidence of NCS in non-neurological patients a general statement to clinical relevance of self-limiting NCS could yet not be given.

It has been hypothesized that the predominant background EEG activity is correlated with the amount of analgo-sedative drugs and serves as a reliable outcome parameter in ICU patients. However, in the present study with 50 patients no correlation between the predominant background EEG activity and the dosage of analgo-sedative drugs has been detected. Possibly the amount of analgo-sedative drugs necessary to reach a Richmond Agitation and Sedation Score of −1 to 0, as the target in the presented patients population, has been too low to interfere with the EEG background activity. Therefore, it is more likely that the depressed background EEG activity in the observed patients may be caused by cerebral dysfunction due to the underlying illness. Additionally, in the present study the predominant background cEEG activity did not correlate with the incidence of delirium or ICU mortality. This is in contrast to investigations in patients with septic shock showing that early suppression of background EEG activity (group 5 in the present observation) and predominant delta activity (group 3 in the present observation) were independent risk factors for incidence of delirium, ICU mortality and 1-year mortality [13,15]. A possible explanation might be that in the present observation the patients were, in contrast to the mentioned studies, hemodynamically stable during cEEG registration. Despite the small amount of patients, it can be suggested, that

suppressed cEEG background activity in hemodynamically stable patients with unexpected unconsciousness may not a reliable predictor for poor outcome.

A limitation of the present observation is the use of only 10 EEG electrodes. While the ESICM recommend 21 electrodes, a further consensus statement recommend 16 electrodes to detect seizures in cEEG by critically ill patients [3,5]. Sensitivity of seizure detection directly correlates with the amount of electrodes [16-18]. However, the time for montage and the handling of the patient's head is increasingly difficult and time-consuming with an increasing number of electrodes which may lead to lower acceptance for this monitoring technique. A reduced montage with 7 electrodes showed a sensitivity and specificity over 90% by allocating these electrodes widely over the scalp [19]. Based on the aforesaid, a reduced montage of 10 electrodes seemed to be a reasonable compromise. One finding during the test period was that both occipital electrodes (O1 and O2) often become dispatched due to the head movements by nursing personal or patient's movement and were, therefore, not used in the present study. The implemented allocation of the electrodes was a compromise between sensitivity and specificity at the one side and easy placement of the electrodes with a long-term stable EEG signal at the other resulting in a well-recognized diagnostically gap. Further limitation was that the analysis of the cEEG recording took place after the recording has been terminated. Therefore, the NCS were not treated with anticonvulsive drugs, except the patient with status epilepticus. To ensure a prospective data analysis the EEG investigators were blinded to the patient's outcome parameter and all performed cEEGs during the time period were included in the study, analyzed and presented in the results. Finally, as the present study only performed cEEG in unexpected unconscious patients, the start of cEEG was in median at day 5 and after initial treatment and stabilization. Therefore, seizure activity during the critical first hours of illness has not been detected.

5. Conclusion

Implementing cEEG measurement over a period of 24 hours in unconscious patients at an anesthesiological ICU is feasible after a short training at an EEG laboratory and instruction of the nursing personal. Processing the raw EEG by the used seizure detection software did not replace analysis of the raw EEG by a specialist, but might highlight awareness to suspect EEG patterns. Therefore, direct or teleconsultation collaboration between ICU and EEG specialists is recommended to allow the meaningful and safe use of cEEG at an anesthesiological ICU. Secondarily, predominant background EEG activity may not a reliable outcome predictor.

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4.5. Epileptic seizure discharges in patients after open chamber cardiac surgery – a prospective prevalence pilot study using continuous electroencephalography (A5).[118]

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* equal contribution

Patienten, die sich einer Herzoperation unterziehen, entwickeln häufig ein Delir, welches das Risiko einer postoperativen Morbidität erhöht und zu einer verminderten Lebensqualität führen kann. Retrospektive Studien zeigen ein gehäuftes Auftreten deliranter Syndrome bei Patienten mit epileptischen Anfällen. In diesen Studien wurden jedoch subklinische Anfälle nicht systematisch erfasst, so dass die tatsächliche Inzidenz epileptischer Anfälle nach einer Herzoperation weiterhin unbekannt bleibt. Das Ziel dieser Arbeit war die Untersuchung der Inzidenz elektroenzephalographisch objektivierbarer epileptischer Anfälle nach elektiver, offener Herzchirurgie.

Diese prospektive, verblindete, monozentrische Beobachtungsstudie untersuchte Patienten, bei denen eine elektive offene Herzklappenrekonstruktion oder -ersatz vorgesehen war. Anästhesie, Operation und postoperative Behandlung verliefen standardisiert und wurden durch die studienassoziierten Untersuchungen nicht beeinflusst. Nach der Operation erfolgte umgehend die Verlegung auf die Intensivstation, auf der die EEG-Überwachung innerhalb der ersten Stunde begann. Die Ergebnisse der bis zu 24 Stunden durchgeführten, kontinuierlichen EEG-Aufzeichnungen wurden von zwei verblindeten, für die EEG-Auswertung zertifizierten Neurologen unabhängig voneinander analysiert.

100 Patienten wurden in diese Studie eingeschlossen. Pathologische EEG-Muster ließen sich bei 33% der Patienten darstellen, 9% aller Patienten boten elektroenzephalographisch detektierbare Anfälle. Die EEG-Grundaktivität zu Beginn jeder Aufzeichnung wurde entweder unterdrückt oder zeigte ein Burst-Suppressionmuster. Am Ende der Aufzeichnungszeit besaßen alle Patienten einen Alpha-/Theta-Grundrhythmus. Eine Assoziation zwischen elektroenzephalographisch detektierbaren Anfällen und einem Delir wurde gefunden ($p\chi 2 < 0{,}01$).

Diese Studie zeigt eine überraschend hohe Inzidenz pathologischer EEG-Muster und elektroenzephalographisch detektierbarer epileptischer Anfälle im frühen postoperativen Verlauf bei Patienten nach einer elektiven, offenen Herzoperation. Da elektroenzephalographisch detektierbare Anfälle mit dem Auftreten eines Delirs assoziiert waren, erscheint dieser postoperative Befund als ein relevantes Phänomen in der herzchirurgischen Intensivpopulation.

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ORIGINAL

Epileptic seizure discharges in patients after open chamber cardiac surgery—a prospective prevalence pilot study using continuous electroencephalography

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Abstract

Purpose: Patients undergoing cardiac surgery often develop delirium which increases the risk of postoperative morbidity and leads to a reduced quality of life. Retrospective studies show a higher incidence of delirium in patients with seizures. However, these studies do not systematically detect subclinical seizures, so the incidence of seizures after cardiac surgery remains speculative. The objective of this study is to determine the prevalence of electrographic seizures after elective open-chamber cardiac surgery.

Methods: This prospective, blinded, monocentric, observational study investigated patients scheduled for elective open-chamber valve reconstruction or replacement. Anaesthesia, surgery and postoperative treatment were standardized and not influenced by the presented observation. After surgery, all patients arrived at the ICU, and EEG monitoring started within the first hour. EEG recording was continuously performed for up to 24 h, and the results were independently analysed by two blinded EEG board-certified neurologists.

Results: 100 patients were included. Abnormal EEG patterns were present in 33% of patients, and 9% of all patients showed electrographic seizures. The main EEG activity at the beginning of each recording was suppressed or showed a burst-suppression pattern, and at the end of recording, all patients had an alpha/theta rhythm. An association between electrographic seizures and delirium was found ($p_{\chi 2} < 0.01$).

Conclusion: This study reveals a surprisingly high incidence of abnormal EEG patterns and electrographic seizures in patients undergoing open-chamber cardiac surgery. As electrographic seizures are associated with the incidence of delirium, this finding is a relevant phenomenon in the post-cardiac surgery ICU population.

Keywords: Electroencephalography, Cardiac surgery, Seizures, Electrographic seizures, Delirium

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Introduction

Patients undergoing cardiac surgery often develop delirium and postoperative cognitive deficits (POCD), which leads to a higher risk of postoperative morbidity and mortality and a reduced quality of life [1]. Retrospective studies show a higher incidence of delirium, stroke and mortality in patients with convulsive and non-convulsive seizures after cardiac surgery [2, 3]. However, these studies consider either clinically obvious, generalised, convulsive seizures or non-convulsive seizures, the latter of which are diagnosed by a corresponding pathological EEG examination, with the indication to perform such an examination remaining uncertain. Overall, these studies indicate an incidence of postoperative epileptic seizures of 1–2.5% but do not systematically investigate the incidence of subclinical seizures in the early postoperative period. Gofton et al. analysed an unselected cardiac surgery collective using a continuous subhairline EEG, finding seizures in 3% of the patients, all of whom underwent open-chamber surgery [4]. However, the use of subhairline electrodes leads to underdiagnosis of seizures [5, 6]. In summary, the incidence of seizures after cardiac surgery remains speculative. Seizures are treatable and, therefore, represent a potential target in the prophylaxis of delirium and POCD.

To investigate the accurate prevalence of seizures, we conducted this prospective study on patients undergoing open-chamber cardiac surgery using continuous EEG monitoring with widely distributed electrodes in a 10-channel registration.

Methods

This prospective, blinded, monocentric, observational study was conducted at Kerckhoff-Hospital, Bad Nauheim, Germany, from January 2016 to December 2017. After gaining approval from the local ethical committee of Justus-Liebig-University Giessen, Germany, and obtaining written informed consent, consecutive patients scheduled for elective open-chamber aortic or mitral valve reconstruction or replacement were included. Exclusion criteria were emergency surgery, lack of informed consent, pregnancy, pre-existing epilepsy, surgery in deep hypothermia or off-pump surgery. Patients were screened for pre-existing cognitive deficits using the mini-mental status examination (MMSE) the day before surgery. The anaesthesia, surgery and postoperative treatment were standardised and not influenced by the presented observation. The anaesthesia induction included 2.5–3 mg/kg propofol and a 0.8–1 µg/kg sufentanil bolus. Propofol was applied continuously, and remifentanil was added at a rate of 0.15–1 µg/kg*min for continuous analgesia. In addition to the continuous remifentanil, sufentanil boli were applied before painful surgical procedures. The target of the bispectral index (BIS) was between 40 and 60.

Take-home message

This study reveals for the first time a surprisingly high incidence of 33% abnormal EEG patterns, including 9% that were electrographic seizures, after open-chamber cardiac valve surgery, which shows an association with the incidence of delirium.

In order to prevent air embolism, CO_2 was inflated into the open heart and air was manually squeezed out at the end of the bypass procedure. Patients were placed in a Trendelenburg position, and the aortic root vent evacuated the air outside of the cavum and the aorta. Transoesophageal echocardiography was used to confirm that no air remained, then the aortal clamp was opened and the patient was positioned horizontally. After surgery, all patients were admitted to the ICU with analgo-sedative drugs (remifentanil and propofol) and invasive ventilation. After the EEG monitoring was established, propofol and remifentanil were tapered with the goal of early extubation. Piritramide and metamizole were used to obtain analgesia.

EEG monitoring started within the first hour after the patients' admission to the ICU (EEG-1100-system, Nihon Kohden Europe GmbH, Rosbach, Germany). An EEG was performed using 10 cup electrodes (Ag/AgCl) fixed at the scalp with electrode paste following abrasion of the skin surface. The electrodes were placed according to the 10–20 system at Fp1, Fp2, C3, C4, P3, P4, T3, T4, Fz and Cz. EEG recording was performed continuously for up to 24 h unless patients were discharged from the ICU or more than three electrodes became dysfunctional. Afterwards, the EEG results were independently analysed with a focus on predominant background EEG frequencies and abnormal EEG patterns, such as periodic discharges, rhythmic delta activity, rhythmic or sporadic spikes, sharp-and-slow-waves, spike-and-wave and electrographic seizures, defined as patterns with evolution in amplitude and frequency, as determined by two EEG board-certified neurologists (MT, PS) [7, 8]. Both were blinded to patients' treatment and outcome parameters. The EEG interpretation was performed after patients' treatment, so the findings had no influence on the individual therapy. In the case of different interpretations, both investigators analysed the individual pattern together until a consensus was reached.

For secondary analysis, the incidence of delirium was assessed by nursing staff on the first and fourth postoperative day using the confusion assessment method for the intensive care unit (CAM-ICU). Furthermore,

the patients' length of stay in the ICU and postoperative strokes up to the end of inpatient rehabilitation were recorded. Dosages of clorazepate for premedication, dosages of tranexamic acid, time of extracorporeal bypass, aortic clamping time, lowest temperature during cardiopulmonary bypass, intraoperative BIS and mean arterial blood pressure were recorded in the anaesthesia protocol and used to detect potentially uncontrollable influencing factors.

Statistical analysis

Due to the absence of preliminary data, a power analysis could not be performed. For this prevalence study, a sample size of 100 patients was aimed. The prevalence of seizures and epileptic discharges was analysed descriptively. For secondary analysis, a classification was performed of patients with/without abnormal EEG pattern and of patients with/without electrographic seizures. It was investigated whether the groups with/without abnormal EEG pattern and with/without electrographic seizures differed in patient characteristics (age, gender, BMI), preoperative mental state or intra-operative data. To verify whether the groups differed significantly in categorical variables, Chi-square tests were calculated on the basis of a dichotomous scale level of the variable. For parametric continuous variables, Student's t tests were used. Continuous variables that did not meet the criteria of parametric testing were evaluated using Mann–Whitney U test. Normal distribution was proven with the Shapiro–Wilk test and variance homogeneity with the Levene test. For all metric variables, mean values and standard deviation (SD) were reported; for categorically scaled parameters, frequency and percentage were given. Statistical analyses were calculated using SPSS (version 24, IBM® SPSS® Statistics, USA). A significance level with $p < 0.05$ was considered to be statistically significant.

Results

One hundred patients were included, 76% of whom underwent aortic valve replacement and 24% of whom endured mitral valve reconstruction or replacement. The mean age of the patients was 70 ± 10 years, 72% were male, and the mean BMI was 27 ± 5 kg/m^2. The American Society of Anesthesiologists' physiological status classification was 3 [2; 4]. The mean MMSE before surgery was 28.3 ± 1.7. All patients who gave consent were measured, with no dropouts after the primary analysis. Clorazepate was used as premedication in 85% of the patients (24 ± 16 mg), and 99% of the patients received tranexamic acid (2.8 ± 0.7 g, max 4.0 g) during the surgery. Extracorporeal circulation was performed for 112 ± 37 min, with aortal clamping times of 76 ± 24 min. EEG recording lasted 12.9 ± 7.2 h per patient, resulting in 1267 h of EEG data. Five patients remained intubated and were mechanically ventilated at the end of the EEG recording. One of them received 30 mg/h propofol. Delirium, as defined by the CAM-ICU, was observed in 9 patients on day 1 (9%) and 9 patients on day 4 (9%). In 5 patients, the delirium existed at both times.

33% of the patients showed abnormal EEG patterns such as periodic discharges, rhythmic delta activity, rhythmic or sporadic spikes, sharp-and-slow-waves and spikes-and-waves (Table 1). In 9 of these patients (9% overall), the EEG pattern showed evolution in amplitude and frequency and was interpreted as having electrographic seizures (Fig. 1). The inter-observer agreement was 86%. None of the patients' seizures were observed by the intensive care staff. The main EEG activity at the beginning of the recording time was suppressed or showed a burst-suppression pattern, presumably due to analgo-sedative medication, whereas at the end of EEG recording, the main EEG activity in all patients was an alpha or theta rhythm.

Secondary analysis revealed that the prevalence of electrographic seizures was associated with the incidence of postoperative delirium on the first postoperative day (relative risk 8.09; 95% confidence interval [2.63; 24.84]; $p_{\chi 2} < 0.01$; effect size $w = 0.388$) and in patients with prolonged delirium at days 1 and 4 (relative risk 6.74; 95% confidence interval [1.29, 35.2]; $p_{\chi 2} = 0.06$). Patients with electrographic seizures were older (78 vs. 69 years; $p = 0.03$) and female (6 f vs. 3 m; $p = 0.01$) and tended to achieve lower results in pre-surgical MMSE, though this did not reach statistical significance (26.9 ± 3.5 vs. 28.5 ± 1.4; $p = 0.08$). The duration of cardiopulmonary bypass, lowest temperature, BIS level and blood pressure due to bypass were not different in patients with abnormal EEG patterns or electrographic seizures. The used dosages of neither clorazepate nor tranexamic acid varied in the observed groups. Four patients had suffered

Table 1 Abnormal EEG findings of the individual patients

Electrographic seizures	9% (9/100)
Generalized rhythmic delta activity (GRDA)	14% (14/100)
Plus superimposed sharp waves/spikes (+S)	5% (5/100)
Plus superimposed fast activity (+F)	3% (3/100)
Generalized rhythmic spike and wave (GSW)	2% (2/100)
Bilateral independent periodic discharges (BIPD)	2% (2/100)
Plus superimposed rhythmic activity (+R)	1% (1/100)
Lateralized rhythmic delta activity (LRDA)	1% (1/100)
Lateralized rhythmic spike and wave (LSW)	3% (3/100)
Sporadic epileptiform discharges	17% (17/100)

Electroencephalography (EEG) findings of the patients with abnormal patterns according to [7, 8]

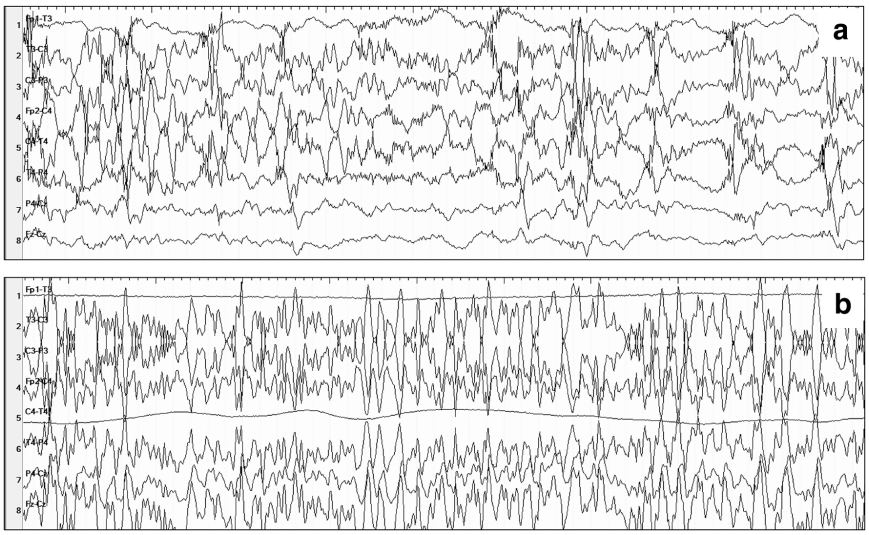

Fig. 1 Exemplary sections of electroencephalograms (EEG) of two patients with electrographic seizures. **a** Section of left focal rhythmic spike- and poly-spike-wave activity. **b** Bilateral rhythmic spikes, poly-spikes and poly-spike-wave activity, with artefacts over T3 and T4

a stroke according to their medical history, but this was not associated with an abnormal EEG pattern ($p=1.00$). Patients were not screened for occult ischemic strokes. Five patients—2/33 with and 3/67 without abnormal EEG patterns ($p=1.00$)—exhibited acute focal neurological symptoms, and ischemic stroke was confirmed by CT or MRI. Delirium compared to no delirium at day 1 was more pronounced in elderly patients (76 vs. 69 years; $p=0.04$). The comparison between patients with and without electrographic seizures is shown in Table 2. The comparison between patients with abnormal EEG patterns, including electrographic seizures, and without abnormal EEG patterns can be reviewed in Table 3.

Discussion

This pilot study shows a surprisingly high prevalence of abnormal EEG patterns after open-chamber cardiac surgery. Electrographic seizures were observed in 9/100 (9%) of patients, and abnormal EEG patterns were observed in 33/100 (33%) of patients. Electrographic seizures had a significant association with postoperative delirium and with higher age. All electrographic seizures had no obvious clinical correlate and were not observed by ICU staff. They, therefore, could only be detected by comprehensive EEG monitoring.

We present, for the first time, prospectively assessed EEG data in a representative population undergoing elective open-chamber cardiac surgery. The prevalence of electrographic seizures is higher than in previously published studies of adult patients [2–4], since here for the first time a prospective EEG measurement with widely distributed EEG electrodes was applied. In neonatal patients undergoing cardiac surgery, a prevalence of electrographic seizures at 8% has been reported [9]. Another study investigating EEGs in sepsis patients described a comparable prevalence of non-convulsive seizures at 11% and periodic discharges at 25%, similar to the findings described here [10]. In principle, sepsis is a systemic inflammatory response to an infectious pathogen, but a systemic inflammatory response also has been observed after cardiopulmonary bypass [11]. Systemic inflammation therefore might be a potential factor leading to abnormal EEG findings and delirium. The current data provide the necessary basis for further investigations regarding the origin and clinical impact of such EEG abnormalities.

This study has some limitations. Patients were not simultaneously monitored by video, and their EEGs were analysed retrospectively. Since there was no continuous observation of the patients, convulsive versus non-convulsive seizures could not be differentiated. On the

Table 2 Comparison between patients with and without electrographic seizures

	Patients with electrographic seizures ($n=9$)	Patients without electrographic seizures ($n=91$)	p value
Gender [f/m]	6/3	22/69	0.01
Age [years]	78 ± 2	69 ± 10	0.03
MMSE	26.9 ± 3.5	28.5 ± 1.4	0.08
Delirium day 1 [*n* (%)]	4 (44%)	5 (6%)	< 0.01
Delirium day 4 [*n* (%)]	2 (22%)	7 (8%)	0.19
Delirium day 1 + 4 [*n* (%)]	2 (29%)	3 (3%)	0.06
Preoperative dose of clorazepate [mg]	16 ± 14	25 ± 16	0.10
AVR/MVR [*n*]/[*n*]	7/2	69/20	1.00
Extracorporeal circulation [min]	114 ± 53	113 ± 36	0.44
Aortal clamping time [min]	74 ± 42	76 ± 22	0.15
Deepest temperature [°F/°C]	95 ± 34/35 ± 1	93 ± 35/34 ± 1	0.53
Time of BIS < 40 [min]	61 ± 23	62 ± 44	0.97
Time of MAP < 40 mmHg [min]	4 [2; 24]	6 [0; 63]	0.98
Doses of tranexamic acid [g]	2.9 ± 0.5	2.7 ± 1	0.55
Lengths of ICU stay [days]	2 [1; 12]	1 [1; 26]	0.08

Values given as mean ± standard deviation, median [min; max] or frequencies (*n*) and percentage. Statistical analysis was performed with Mann–Whitney *U* test, Pearson or Fisher Chi-square test

EEG electroencephalogram, *f* feminine, m masculine, *MMSE* mini-mental status examination, *AVR* aortic valve replacement, *MVR* mitral valve replacement or reconstruction, *BIS* bispectral index, *MAP* mean arterial blood pressure, *ICU* intensive care unit

Table 3 Comparison between patients with and without abnormal EEG pattern

	Patients with abnormal EEG ($n=33$)	Patients without abnormal EEG ($n=67$)	p values
Gender [f/m]	10/23	18/49	0.72
Age [years]	71 ± 9	69 ± 10	0.17
MMSE	28 ± 2	28 ± 1	0.47
Delirium day 1 [*n* (%)]	5 (15%)	4 (6%)	0.15
Delirium day 4 [*n* (%)]	5 (15%)	4 (6%)	0.16
Delirium day 1 + 4 [*n* (%)]	3 (9%)	2 (3%)	0.33
Preoperative dose of clorazepate [mg]	24 ± 16	23 ± 16	0.74
AVR/MVR [*n*]/[*n*]	27/5	49/17	0.26
Extracorporeal circulation [min]	114 ± 48	112 ± 32	0.43
Aortal clamping time [min]	76 ± 31	76 ± 19	0.35
Deepest temperature [°F/°C]	93 ± 36/34 ± 2	93 ± 34/34 ± 1	0.67
Time of BIS < 40 [min]	64 ± 51	61 ± 39	0.73
Time of MAP < 40 mmHg [min]	4 [0; 27]	6 [0; 63]	0.5
Doses of tranexamic acid [g]	2.9 ± 0.5	2.7 ± 0.8	0.42
Lengths of ICU stay [days]	1 [1; 12]	1 [1; 26]	0.65

Values given as mean ± standard deviation, median [min; max] or frequencies (*n*) and percentage. Statistical analysis was performed with Mann–Whitney *U* test, Pearson or Fisher Chi-square test

EEG electroencephalogram, *f* feminine, *m* masculine, *MMSE* mini-mental status examination, *AVR* aortic valve replacement, *MVR* mitral valve replacement or reconstruction, *BIS* bispectral index, *MAP* mean arterial blood pressure, *ICU* intensive care unit

other hand, the intensive care staff did not register any convulsive seizures. Artefacts by passive or active movement of the patients also were not marked in the EEG. The EEG analyser, therefore, widely ignored patterns typical for active or passive movements. The influence of electrographic seizures or abnormal EEG patterns on outcome parameters, on the one hand, and the influence of perioperative procedures on such EEG abnormalities, on the other hand, cannot be calculated, as this study was not powered for this purpose. All described secondary

calculations in this trial are, therefore, narrative at this point and should be reproduced and systemically evaluated in the context of further studies.

This study was created as a preliminary pilot study to detect the prevalence of EEG abnormalities in the observed population. Therefore, the study was not powered to investigate the relationship between abnormal EEG patterns and secondarily assessed parameters. However, a significant association between electrographic seizures and delirium exists, supporting the hypothesis of a relationship. Delirium occurred in 9% of patients and was, therefore, considerably less frequent than the 24% prevalence in the mixed cardiac surgery population described in previous studies [12]. This observation can likely be explained by the fact that delirium assessment in the above-mentioned investigation was carried out at specific times by specially trained staff, whereas in this study, it was done in the context of routine patient care by intensive care and nursing staff who might underestimate the occurrence of hypoactive delirium, which can be harder to identify. Electrographic seizures and delirium were more pronounced in elderly patients. Furthermore, patients presenting electrographic seizures tended to have lower MMSE level prior to surgery, though this did not reach statistical significance. Both age and preexisting cognitive impairment are well-known risk factors for delirium in ICU patients [13]. It should be discussed whether both entities—seizures and delirium—may be independent consequences of major surgery on an aged and potentially already impaired brain. The association between abnormal EEG patterns and delirium in elderly patients should be investigated in further studies, implementing additional assessments for POCD. Assessing POCD is time-consuming and places high demands on personnel resources. To avoid underpowering in POCD studies, a valid power analysis is necessary. Due to the lack of robust prevalence data on seizures in the population of interest, this investigation was performed without postoperative neurocognitive examinations. POCD is defined as a decline in performance in neuropsychological tests relative to preoperative performance. Its frequency strongly depends on the follow-up interval and the applied diagnostic criteria [14]. Cognitive deficits are still measurable in 16–23% of patients three months after the operation and in 31% of patients undergoing cardiac bypass surgery even after 3 years [15, 16]. Patients with status epilepticus or repetitive epileptic seizures are known to experience persistent cognitive deficits in memory and learning even one year after the event [17]. Accordingly, the prevalence of delirium and electrographic seizures in this study now enables the performance of a power analysis in further studies; for the investigation of an association between delirium and electrographic seizures, a sample size of 73 patients should be aimed for (alpha 0.05; power 0.8; effect size $w = 0.388$). In particular, since seizures are potentially treatable with anticonvulsive drugs, the detection and, if necessary, treatment of early postoperative seizures might be of great clinical importance for the incidence of POCD and will be investigated in further trials.

Conclusions

Postoperative delirium and POCD are relevant complications of open-chamber cardiac surgery. The underlying pathophysiology is largely unknown and most likely multifactorial. The present study reveals for the first time a high incidence of abnormal EEG patterns and clinically silent postoperative electrographic seizures, with an association of the latter to delirium incidence. This finding warrants further studies to determine whether postoperative abnormal EEG activity contributes to prolonged delirium and POCD and, thus, might represent a promising target for perioperative neuroprotection.

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Author contributions

The study was designed by PS, TG and MS. Material preparation, data collection and analysis were performed by MT, MJ, PS, FA, MB, JES and MM. EEG analysis was performed by MT and PS. Statistical analyses were performed by MB. The first draft of the manuscript was written by PS, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Compliance with ethical standards

Conflicts of interest

The authors declare that they have no conflict of interests.

Ethics approval

Approval of the ethical committee of the Justus Liebig-University Giessen, Germany, approval number 159/14.

Consent to participate

The written informed consent was obtained from all patients.

Availability of data and materials
All data generated or analysed during this study are included in this published article and its supplementary information files.

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4.6. The Relevance of postoperative Cognitive Decline in Daily Living: Results of a 1-Year Follow-up (A6).[119]

Sabrina Kastaun, Tibo Gerriets, Niko P. Schwarz, Mesut Yeniguen, Markus Schoenburg, Christian Tanislav, Martin Juenemann

Postoperative kognitive Defizite (POCD) üben einen wahrnehmbaren Einfluss auf das tägliche Leben der Betroffenen aus und scheinen drei Monate nach dem Aortenklappenersatz häufiger von nahen Verwandten als von den Patienten selbst bemerkt zu werden. Ziel dieser Studie war es, den Längsschnittverlauf der subjektiven Wahrnehmung postoperativer kognitiver Defizite aufzuklären.

Diese prospektive Beobachtungsstudie wurde monozentrisch in der Klinik für Herzchirurgie der Kerckhoff-Klinik Bad Nauheim durchgeführt. 108 Patienten, die sich einem offenen Aortenklappen-Ersatz unterzogen sowie 85 Angehörige wurden eingeschlossen. Zusätzlich zu einer neuropsychologischen Untersuchung befragten die Autoren zuvor 82 Patienten mit einem Fragebogen zur Selbsteinschätzung der Häufigkeit im Alltag begangener Fehler (Cognitive Failure Questionnaire, Selbstbeurteilung, s-CFQ) und 62 nahestehende Angehörige mit einem entsprechenden Instrument zur Fremdbeurteilung dieser Alltagsfehler (Cognitive Failure Questionnaire for others, Fremdbeurteilung, f-CFQ) vor und 3 Monate nach der Operation. Bis 12 Monate nach der Operation befragten die Autoren kontinuierlich weitere Patienten, wodurch die ursprüngliche Stichprobe vergrößert wurde, und schlossen die gesamte Gruppe (108 Patienten, 85 Angehörige) für die 12-monatige Nachbeobachtung ein.

Die Analyse zeigte, dass sowohl Angehörige ($p = 0,026$) als auch Patienten selbst drei Monate nach der Operation kognitive Defizite seitens des Patienten wahrnehmen ($p = 0,009$) und in diesem Zusammenhang sowohl Gedächtnis- als auch Aufmerksamkeitsstörungen im Mittelpunkt stehen. Nach einem Jahr unterschied sich die Selbstbeurteilung durch den s-CFQ nicht mehr vom präoperativen Status. Die Durchschnittswerte im f-CFQ lagen zwar immer noch über dem Ausgangswert, waren statistisch jedoch nicht signifikant ($p = 0,051$). Bei Patienten mit einer "Verschlechterung" des f-CFQ im 1-Jahres Follow-Up, konnten 3 Monate postoperativ kognitive Defizite im Bereich des nonverbalen Lernens beobachtet werden ($p = 0,021$). Nur eine Abnahme des 3-Monats-f-CFQ korrelierte mit einem Rückgang spezifischer neuropsychologischer Testergebnisse 3 Monate nach der Operation.

Die vorliegenden Daten zeigten einen deutlichen und relevanten subjektiven Einfluss postoperativer kognitiver Defizite auf die Alltagsfunktionen, der sowohl von Patienten als auch von Angehörigen wahrgenommen wurde. Im Gegensatz zur Selbsteinschätzung stimmten die von

Angehörigen erhaltenen Langzeitinformationen über kognitive Defizite besser mit objektiven Testergebnissen überein, was darauf hindeutet, dass es sich um eine zuverlässigere Quelle handelt. Die Ergebnisse dieser Studie betonen die Bedeutung einer kombinierten internen und externen Bewertung kognitiver Defizite bei der Beurteilung der POCD.

The Relevance of Postoperative Cognitive Decline in Daily Living: Results of a 1-Year Follow-up

Sabrina Kastaun, Dipl.Psych,*† Tibo Gerriets, MD,*‡ Niko P. Schwarz, PhD,*§ Mesut Yeniguen, MD,*‡ Markus Schoenburg, MD,† Christian Tanislav, MD,* and Martin Juenemann, MD*‡

Objectives: **Postoperative cognitive decline (POCD) has a perceivable influence on daily living and is noticed more often by close relatives than by patients themselves 3 months after aortic valve replacement. This study aimed to elucidate the longitudinal course of the subjective awareness of POCD.**

Design: **Follow-up of a prospective observational study.**

Setting: **A single cardiothoracic center in Germany.**

Participants: **The study included 108 patients scheduled for elective aortic valve replacement surgery and 85 close relatives of the patients.**

Interventions: **In addition to conducting a neuropsychologic examination, the authors previously interviewed 82 patients with a Cognitive Failure Questionnaire for self-assessment (s-CFQ), and 62 relatives with the Cognitive Failure Questionnaire for others (f-CFQ) before and 3 months after surgery. Up until 12 months after surgery, the authors continuously interviewed additional patients (baseline and 3 months after surgery), thereby enlarging the original sample, and included the entire group (108 patients, 85 relatives) for the 12-month follow-up.**

Results: **The analysis showed that relatives ($p = 0.026$) and patients experienced patients' cognitive decline 3 months after surgery ($p = 0.009$). All changes still were observed in questions related to memory and attention. After 1 year, the s-CFQ no longer differed between baseline and postoperative assessment. Mean scores in the f-CFQ still were above baseline, barely missing statistical significance ($p = 0.051$). In patients with "change to worse" in the f-CFQ at 1-year follow-up, declining cognitive results in nonverbal learning ($p = 0.021$) could be observed 3 months postoperatively. Only a decrease in 3-month f-CFQ correlated with a decline in specific neuropsychologic tests 3 months after surgery.**

Conclusions: **Contrary to the authors' previous results, the impact of POCD on daily living functions also was recognized by the patients themselves. The long-term influence and the associations between subjective deficits and psychometric cognitive measures seemed to be assessed more reliably by close relatives.**

KEY WORDS: aortic valve replacement, postoperative cognitive deficits, assessment by others, 1-year follow-up

SOON AFTER ON-PUMP cardiac surgeries began in the 1950s, neurologic and neuropsychologic complications (in particular, cognitive deficits) were postulated as postoperative side effects.[1] It has been shown that postoperative cognitive decline (POCD) is related to multiple factors, such as age, cerebrovascular risk factors, or intraoperative microembolism, and that surgical strategies and the use of filter devices may reduce these side effects.[2-4] Neuropsychologic testing can identify POCD on an objective level, and findings from one of the most important longitudinal studies by Newman et al could establish the persistence of these measurable deficits over months and years after surgery.[5]

Although clinicians often are confronted with subjective complaints about cognitive deficits from patients or close relatives, the influence of declining psychometric results on daily living has remained unclear for a long time. Several studies have indicated an increase of self-reported memory complaints after cardiac surgeries,[6-8] but the reliability of self-reported cognitive deficits remains questionable. A previous study from the authors' research group assessed cognitive failures as recognized by patients and close relatives before and 3 months after aortic valve replacement on a quantitative level and demonstrated a perceivable impact of POCD on daily living functions. The main findings included that slight deficits were noticed more often by close relatives (eg, spouses) than by the patients themselves, and only correlations between spouses' estimations and patients' psychometric measures were demonstrated. These data led to the conclusion that assessment of POCD by others was more reliable than self-assessment.[9]

To date, only 1 other study has focused on external assessment. Bergh et al[8] reported on a decline in memory functions after coronary artery bypass grafting and angioplasty perceived by patients and spouses. Unfortunately, the data were collected retrospectively 1 to 2 years after intervention; thus, there was no baseline status determined or neuropsychologic tests performed to objectively quantify cognitive decline. Hence, it still remained unclear whether POCD, objectified by neuropsychologic testing, could have a verifiable long-term influence on daily living as perceived by close relatives or patients themselves.

The authors now report on their findings of the 1-year follow-up, aiming to elucidate the longitudinal course of postoperative subjective complaints after aortic valve replacement compared with baseline levels and the objective cognitive measures 3 months after surgery. In light of the previous findings, the authors expected relatives to be a more reliable source of information than patients on cognitive decline even 1 year after surgery.

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PATIENTS AND METHODS

Enrollment

The study design has been described previously.[9] Referring to differences in neuropsychologic pretests to post-tests from other studies,[6,7,10] in the original study, medium effect sizes ($r = 0.3$-0.4) were expected. With a chosen significance level of $\alpha = 0.05$, between 40 and 60 patients would be needed to reach a power level of 0.85. A dropout rate of 20% to 30% was anticipated due to experiences in such clinical studies.

In the original study, 82 patients and 62 relatives were enrolled for the evaluation of short-term POCD. While arranging the 1-year follow-up, the authors continued recruiting patients, increasing the sample by 26 patients. Finally, 108 patients who were scheduled for elective aortic valve replacement surgery were included in this study and underwent 1-year follow-up.

All patients were medically stable at inclusion. The exclusion criteria were defined as a history of stroke and psychiatric or neurologic disorders. Patients had to complete a psychometric cognitive test within 2 weeks (± 1 week) before surgery and were reassessed 3 months (± 1 week) after surgery. At the same intervals, and additionally 12 months (± 2 weeks) after surgery, patients completed a questionnaire related to cognitive failures by self assessment, and cognitive failure questionnaires for assessment by others were addressed to relatives of the patients and sent in the mail. Twenty-three relatives did not answer at least 1 questionnaire in a correct manner (eg, omitted their names) or refused or forgot to send back the questionnaires; these studies were excluded from the statistical analysis. Finally, 85 close relatives (54 female, 31 male) of the patients completed the Cognitive Failure Questionnaire for others (f-CFQ) 3 months after the surgery and at 1-year follow-up. Most of the relatives were spouses or long-term partners (87.0%); only 9 children (10.6%) and 2 siblings (2.4%) completed the questionnaires.

This study complied with the Declaration of Helsinki and was approved by the ethics committee of the Justus Liebig University Giessen. All participants gave signed informed consent.

Surgery

Ninety-two patients received biologic valves and 16 mechanical valves. Oral anticoagulation for mechanical valves included dose-adjusted usage of vitamin K antagonists.

After premedication with flunitrazepam, total intravenous general anesthesia was induced and maintained using sufentanil and propofol. No volatile anesthetics were used. After relaxation with pancuronium bromide, the trachea was intubated and controlled with normocapnic ventilation with an air/oxygen mixture. Standard monitoring was applied, including pulse oximetry, mainstream capnometry, peripheral and central body temperature sensors, and arterial and pulmonary artery catheters. Arterial blood gas, electrolyte, and glucose levels, and activated clotting time were measured repeatedly according to the authors' standard anesthesia protocol.

All procedures were performed using conventional full median sternotomy under cardiopulmonary bypass and mild hypothermia (32-34°C). The dynamic bubble trap was integrated into a standard extracorporeal circulation (ECC) tubing set containing a 40-μm heparin-coated arterial line filter. Extracorporeal perfusion was performed using a roller pump and a hollow-fiber membrane oxygenator with a venous hard-shell reservoir at a nonpulsatile flow rate of 2.4 L/min/m^2. The circuit was primed with 1,600 mL of Ringer's solution, 100 mL of mannitol 20%, 100 mL of sodium bicarbonate 8.4%, 5,000 U of heparin, and 2 mL of aprotinin.

Standard cannulation technique was performed with a wire inlay aortic arch cannula, which was placed in the ascending aorta, and with a proximal and distal wire-reinforced 2-stage venous cannula through the right atrium. After systemic heparinization (500 U/kg), ECC was initiated according to the alpha-stat concept. Additional heparin was added during cardiopulmonary bypass to maintain the activated clotting time above 400 seconds if necessary. The left ventricle was vented using an aortic root cannula. Blood cardioplegia was injected antegrade in the aortic root and retrograde in the coronary sinus to achieve and sustain cardiac arrest. After the aorta was opened through vertical incision and the aortic valve was exposed, excision and measurement of the new valve and implantation with supported sutures were performed.

After the aortotomy was closed, the aorta and left ventricular chamber were de-aired carefully using aortic root cannula and puncture of the left ventricular tip under constant lung inflation. The cross-clamp then was removed. Thereafter, the patients were weaned from ECC. After myocardial function returned and the patients reached normothermic conditions, ECC was terminated. Intraoperative echocardiography was used to assess residual air and ventricular function in every patient.

Questionnaires

Study participants completed a validated German version of the Cognitive Failure Questionnaire for self assessment (s-CFQ)[11] or the f-CFQ.[12] The questionnaires evaluate the frequency of failures in daily living related to memory, attention, action, and perception. Because memory impairment is most pronounced in POCD, the s-CFQ was modified slightly, with additional items related to memory failures, which were taken from the validated German version of the Memory Complaint Questionnaire.[13] All scores were summarized in a global sum score for both questionnaires (maximum score s-CFQ = 116, maximum score f-CFQ = 32). Furthermore, because the s-CFQ is more extensive, items were included in a factor analysis with varimax rotation.[14] Because the results did not show additional meaningful outcomes in the main analysis, only global sum scores were presented. To score depression and anxiety, the validated German version of the Hospital Anxiety and Depression Scale (HADS) was used.[15] In all questionnaires, higher scores represented worse outcomes.

Neuropsychologic Assessment

Cognitive examination was performed using a battery of well-established and validated tests 1 to 4 weeks before cardiac surgery and 3 months (± 1 week) after intervention. The tests always were administered by the same psychologist. In all domains, parallel test forms were used at follow up to account

for learning effects. Attention was examined using a number cancellation test. The patient was asked to cross out all target numbers on a test sheet, and the time the patient needed to finish this task was measured. Word fluency as a component of executive functioning was examined using the Regensburg Word Fluency Test.[16] The patient needed to generate words with alternately changing initial letters (eg, G/H).

Visual memory was examined using the Non-Verbal Learning Test[17] and the pictorial memory subtests of the German Syndrom-Kurztest.[18] In the Non-Verbal Learning Test, a variety of 120 cards showing abstract symbols were presented to the patient, who was asked to recognize particular target symbols. In the Syndrom-Kurztest, the patient needed to recall objects of a picture list and, after a delay, to detect the particular objects in a choice list of pictures. Verbal memory was examined using the delayed recognition list of a verbal learning and recognition test,[19] a modified German version of the Rey Auditory Verbal Learning Test.[20] A list of 15 words was read to the patients in 5 trials, and a choice list was read to the patients approximately 30 minutes after the first learning trials. False responses were subtracted from the total sum.

Statistics

Normality of distribution was tested using the Kolmogorov-Smirnov test and homogeneity of variance using Levene's test. Follow-up scores versus baseline scores were analyzed by using *t*-test for paired samples. For the before-to-after intervention analysis, the effect of potential confounder variables (eg, depression) was controlled by analysis of covariance in a general linear model with repeated measures. Pearson correlation coefficients were used to describe associations between variables. Group differences were calculated with unpaired *t*-tests, and for the primary endpoints, effect sizes were computed from the value of *t* by using the product-moment correlation *r*.[21] The global α-criterion was set at $p = 0.05$. All of the analyses were performed using SPSS Statistics 21 (IBM Corp, Armonk, NY). Post-hoc power analysis was performed using G*Power Version 3.1.7.[22]

RESULTS

Demographic and medical variables are presented in Table 1. Data represent the entire sample of 108 patients, all of whom completed neuropsychologic testing at baseline and 3 months after surgery. Regarding demographic and medical variables, no group differences between the original sample ($n = 85$)[9] and the enlarged sample were found (all $p > 0.05$).

Table 1. Baseline Demographic and Medical Characteristics

Baseline	Value
Age, M ± SD (yr)	68.7 ± 9.2
Males, n (%)	68 (63.0)
Diabetes mellitus, n (%)	20 (18.5)
Arterial hypertension, n (%)	80 (74.0)
Hypercholesterolemia, n (%)	48 (44.4)
Obesity (BMI ≥30 kg/m^2), n (%)	25 (23.1)
Left heart failure (NYHA class II-IV), n (%)	21 (19.4)
Surgery	
Total duration, M ± SD (min)	176.4 ± 48.2
CPB duration, M ± SD (min)	89.3 ± 30.6
Duration of aortic clamping, M ± SD (min)	65.5 ± 24.1

Abbreviations: M, mean; SD, standard deviation; BMI, body mass index; NYHA, New York Heart Association; CPB, cardiopulmonary bypass.

Neuropsychologic Scores

Comparable to the authors' previous analysis with the smaller sample size,[9] POCD occurred in all tests assessing declarative memory functions; the mean performance dropped from baseline in these tests (p values ranging from 0.05 and <0.001) (Table 2). In other tests or domains, no change from baseline was observed.

Questionnaires Scores

In contrast to the first analysis with the smaller sample size,[9] the s-CFQ now differed between baseline and 3-month postoperative assessment (baseline: mean 34.43, standard deviation [SD] 12.93; postintervention: mean 36.64, SD 12.43; $t[0.05; 107] = -2.69$, $p = 0.009$; $r = 0.25$) (Fig 1).

The assessment by others still varied between baseline and 3-month postoperative assessment (baseline: mean 8.81, SD 4.67; postintervention: mean 10.26, SD 5.80; $t[0.05; 84] = -2.27$, $p = 0.026$; $r = 0.24$) (Fig 2). All changes were observed in questions related to memory and attention failures.

Regarding the follow-up evaluation 1 year after surgery, the s-CFQ no longer differed between baseline and postoperative assessment (baseline: mean 34.43, SD 12.93; postintervention: mean 35.10, SD 14.24; $t[0.05; 103] = -0.11$, $p = 0.913$; $r = 0.01$). Mean scores in the f-CFQ still were above baseline, barely missing statistical significance (baseline: mean 8.81, SD 4.67; postintervention: mean 10.18, SD 4.77; $t[0.05; 81] = -1.98$, $p = 0.051$; $r = 0.22$).

After surgery, in the HADS, patients showed declines in depression and anxiety scores compared with the preoperative baseline assessment (depression scores—baseline: mean 4.77, SD 2.99; postintervention: mean 3.70, SD 2.63; $t[0.05; 105] = 2.92$, $p = 0.005$; $r = 0.27$); (anxiety scores—baseline: mean 6.91, SD 3.52; postintervention: mean 5.52, SD 3.41; $t[0.05; 105] = 4.21$, $p = 0.000$; $r = 0.38$). These results were comparable with the authors' first analysis.

Associations Between Cognitive Test Scores, Depression, Anxiety, and Cognitive Failure Questionnaires

Comparable with the first analysis with the smaller sample size,[9] higher (ie, worse) rates in f-CFQ change scores 3 months (change score: mean 1.95, SD 8.44) after surgery correlated with worse results in a few neuropsychologic change scores. Patients whose relatives stated more cognitive failures postoperatively tended to have worse results in the nonverbal learning test (change score: mean 1.23, SD 5.17, $r = 0.76$; $p = 0.008$) and word fluency (change score: mean 1.07, SD 4.18, $r = 0.21$; $p = 0.038$), confirming the results of the authors' previous analysis. No association was found between 3-month postoperative neuropsychologic change scores and cognitive failures stated by close relatives (f-CFQ) 12 months after surgery.

Table 2. Neuropsychologic Data

Test	Pre/Post	Mean	SD	Mean Diff.	SD Diff.	*t* Value	Df	p Value	"Change to Worse?"
SKT-immediate recall*	Pre	5.60	1.48						Yes
	Post	6.08	1.26	–0.48	1.61	–3.11	107	0.002	
SKT-delayed recall*	Pre	6.90	1.63						Yes
	Post	7.34	1.54	–0.44	1.99	–2.05	107	0.050	
SKT-recognition*	Pre	1.14	1.22						Yes
	Post	2.16	1.89	–1.02	1.79	–5.90	107	<0.001	
Nonverbal learning test†	Pre	12.65	3.38						Yes
	Post	11.42	3.88	1.23	5.17	2.48	107	0.015	
Verbal learning test†	Pre	9.16	4.04						Yes
	Post	7.10	4.92	2.06	4.33	4.93	107	<0.001	
Word fluency test†	Pre	15.07	5.33						No
	Post	14.75	5.62	0.36	4.71	0.78	107	0.434	
Number cancellation test‡	Pre	10.28	3.60						No
	Post	10.71	4.07	–0.44	3.94	–1.15	107	0.254	

Abbreviations: SD, standard deviation; mean diff, mean of difference; SD diff, standard deviation of difference; df, degrees of freedom; "change to worse?" indicates statistical difference to baseline with worse postoperative performance; SKT, Syndrom-Kurztest.

*Mean scores represent mistakes.

†Mean scores represent correct answers.

‡Mean scores represent performance time.

For the s-CFQ changes scores 3 and 12 months after surgery, no correlations with the neuropsychologic change scores 3 months after surgery were observed.

During further post-hoc analysis, s-CFQ and f-CFQ change scores from baseline to 3 months after surgery and from baseline to 12 months after surgery were dichotomized into change scores >1 SD (defined as "change to worse") and change scores <1 SD (defined as "no change to worse"). In patients with subjective "change to worse" in s-CFQ at 3- and 12-month follow-up, no relevant cognitive decline was observed within the neuropsychologic assessment 3 months after surgery.

In line with the first analysis, patients with f-CFQ change scores >1 SD (assessed by others) 3 months postoperatively clearly had worse outcomes in word fluency ($t[0.05; 84] = -2.26$, $p = 0.026$) and nonverbal learning ($t[0.05; 84] = -2.83$, $p = 0.001$) at the same time. Furthermore, in patients with "change to worse" in f-CFQ estimation by their spouses at 12-month follow-up, declining cognitive results in nonverbal learning ($t[0.05; 81] = -2.36$, $p = 0.021$) could be observed 3 months after surgery (Fig 3).

No correlations between the change scores in the s-CFQ and f-CFQ 3 and 12 months postoperatively and anxiety or depression scores at 3 months after surgery were found.

DISCUSSION

Previously published data by the authors on the perception of POCD within the first 3 months after intervention indicated that cognitive side effects were noticed more frequently by relatives than by patients themselves.[9] This study referred to

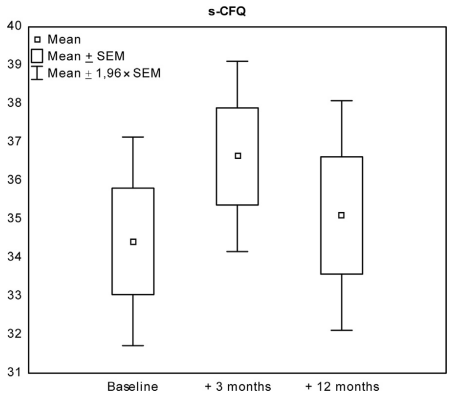

Fig 1. Mean scores (± ranges) that indicated higher (worse) ratings of cognitive failures in daily living perceived by the patients themselves at 3 months after cardiac surgery ($p = 0.009$). SEM, standard error of the mean.

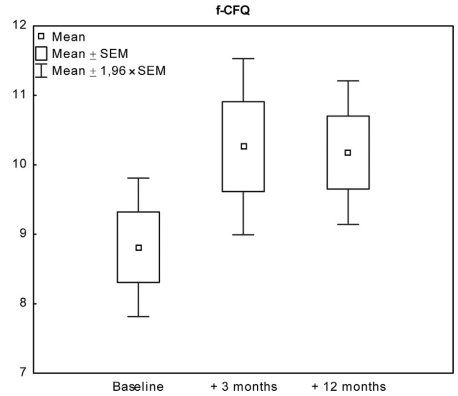

Fig 2. Mean scores (± ranges) that indicated higher (worse) ratings of cognitive failures in daily living perceived by others at 3 and 12 months after cardiac surgery ($p = 0.026$; $p = 0.051$). SEM, standard error of the mean.

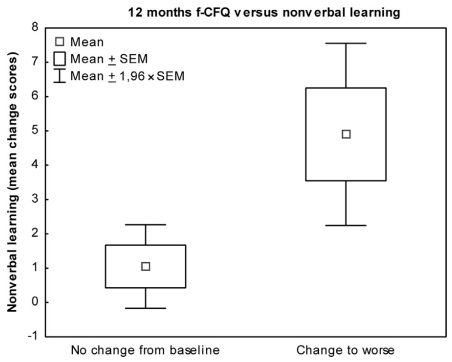

Fig 3. Box-and-whisker plots with mean change scores (± ranges) from neuropsychologic baseline performance versus dichotomized outcome of f-CFQ change from baseline to worse (>1 SD)/no change at 12-months follow-up. In patients with "change to worse" in f-CFQ estimation by their spouses at 12-months follow-up, declining cognitive results in nonverbal learning (p = 0.021) 3 months postoperatively were observed. SEM, standard error of the mean.

findings of the 1-year follow-up on the basis of an increased patient sample.

In accordance with previous studies, neuropsychologic testing indicated POCD in all tests referring to declarative memory functions, in which the mean test performance clearly dropped from baseline values.[4,10,23] Contrary to the authors' previously published results, with a majority of patients being unaware of new memory difficulties, self-assessment of cognitive function in relation to baseline values now demonstrated that patients themselves seemed to recognize cognitive impairment after 3 months.

However, with respect to the long-term data at 1-year follow-up, this difference did not yield statistical significance anymore (see Fig 1). In a prospective study, Keizer et al[24] investigated self-reported cognitive failures in 81 coronary artery bypass grafting patients before and 1 year after surgery using the s-CFQ and, correspondingly, found no substantial proportion of subjective cognitive decline in this setting. Furthermore, internal evaluation of 112 healthy control subjects showed even more cognitive failures compared with the patient cohort. These observations legitimately questioned the reliability of self-reported cognitive deficits. The discussion of possible causes of this difference included the assumption that compared with patients with POCD, mentally healthy subjects rather may be aware of even slight cognitive deficits because the cognitive decline itself can have a negative influence on self-perception and the capability to notice deficits. In addition, the survival of life-threatening diseases and a vitally important surgery might change a patient's valuation of the significance of cognitive decline in daily life, thus leading to underreporting of these deficits.[24]

Although close relatives usually share important life events and large parts of medical and life history of patients, their external evaluation might involve a more objective assessment and might be more sensitive for everyday, relevant cognitive failures with functional impact. Previously published data of this study could demonstrate that POCD 3 months after on-pump cardiac surgery was often and more reliably perceived by close relatives, such as spouses.[9] Herein, follow-up data were analyzed to determine whether potential long-term complaints also were more reliable when detected by close relatives of the patients and whether there was an association with the cognitive decline in psychometrical measures 3 months after surgery.

Mainly attributed to memory and attention failures, the assessment of cognitive function by others significantly worsened after 3 months and, in contrast to the self-evaluation, still at least tended to be worse 1 year after surgery (see Fig 2; p = 0.051). Bergh et al[8] investigated external and internal perceptions of cognitive functions between 1 and 2 years after coronary artery bypass grafting and reported that patient and spouse ratings agreed with each other on memory decline within this timeframe. However, their retrospective study included neither a baseline status nor neuropsychologic tests to objectify cognitive complaints.

The prospective design of the study presented here, with repeated neuropsychologic testing and questionnaire follow-up, enabled correlation of internal and external assessment and evaluation of their quality with respect to potentially measurable dimensions of POCD: F-CFQ assessment after 3 months correlated with worse results in neuropsychologic tests involving nonverbal learning or word fluency. However, no association was found between 3-month postoperative neuropsychologic change scores and cognitive failures as stated by close relatives 12 months after surgery. Both for the 3- and 12-month follow-up, s-CFQ changes showed no relation to the neuropsychologic change scores 3 months after surgery. These findings might lend further support to the observation that short-term POCD (ie, 3 months after surgery) is recognized more reliably by relatives than by patients. After 1 year, relatives tended to recognize POCD more than patients themselves, but this trend did not yield statistical significance. Beyond that, correlations with neuropsychologic tests failed to prove that this subjective view by others was associated with objective POCD.

Several studies have stated an association of subjective cognitive decline after cardiac surgery with disturbances of mood and attributed this phenomenon to an underlying depression.[25,26] In this study, HADS showed reduced depression and anxiety after surgical treatment, and no correlation could be observed between s- and f-CFQ after 3 and 12 months and HADS at 3 months, indicating that self- and externally-assessed worsening of memory function could not be explained by these psychiatric symptoms, which was supported by previous investigations that controlled for depression and anxiety.[6,7,9]

A recently published article by Nadelson et al[27] reviewed the perioperative cognitive trajectory in adults in connection with surgery and associated anesthesia, most notably in cardiac and orthopedic surgery. Although discussed as controversial, postoperative cognitive improvement (POCI) up until 12 months after surgery has been described, after a transient period of postoperative cognitive decline, especially when surgery was successful and could improve previously existing disorders and complaints, such as pain, inflammation, and immobility. Authors underlined that this observation could be attributed to a net cognitive improvement or to a slowing or

arresting of preoperative decline.[27] Although the authors of the study presented here observed single values with a discrete improvement, this study was not designed to detect POCI systematically, and this aspect has not been addressed by a separate statistical evaluation. Provided that surgical interventions aim to improve the quality of life of patients, future studies should consider POCI as a possible postoperative course that might possess the ability to provide valuable approaches to the concept of salutogenesis.

Limitations of this study may have included the study design with an additional recruitment of 26 patients after publication of short-term data that, in the end, led to an alteration of previous results. Although this approach might not be "state of the art," the authors determined that publication of these data would be useful because they may supplement or correct preliminary results of their investigation.

In this study, moderate effect sizes of $r = 0.25$ and $r = 0.24$ were found for the statistically significant declines of cognitive abilities 3 months after surgery assessed by the patients themselves and their relatives. The post-hoc power calculation showed a sufficient power level of 0.73. Given the obtained differences and moderate effect sizes in the present cognitive pre-to-post examination, between 130 and 150 patients would be needed to improve the test power up to a level of at least 0.85 and therefore reduce the type-II error. In the end, continuation of enrollment increased the statistical significance in a previously underpowered study, underlining the necessity of an adequate sample size to detect relevance of POCD and its self-assessment in everyday life. With a view to the parameters for the f-CFQ scores from baseline to 3 months after surgery ($t = -2.2$, $r = 0.24$, $p = 0.026$), where the authors found a statistically significant difference; from baseline to 12 months ($t = -1.9$, $r = 0.22$, $p = 0.051$), and the fact that the persistence of objectified POCD for months and even years after surgery has been documented repeatedly,[5,28] it seems at least debatable whether a slightly increased number of relatives (increased power) after 12 months also would have proven the detected differences in the subjective perception of POCD by close relatives to be statistically significant.

Furthermore, perception of cognitive decline after 12 months had to be compared with results of the neuropsychologic assessment after 3 months. The study hospital takes its patients from a comparatively large geographic area, which includes long journeys for patients, and because personal presence is crucial for neuropsychologic assessment, the authors assumed that the logistical effort for a 12-month follow-up would have led to an increased dropout rate.

The fact that POCD typically occurs during an exceedingly vulnerable period of life, quickly leading to loss of independence and promoting need for long-term care,[29] poses a substantial challenge not only to patients and relatives but also to the healthcare system. Cognitive functions are a substantial and integral part of human self-perception. Consequently, the corresponding impairment has a strong impact on daily routine and constitutes a far-reaching and profound disability. This study's findings may contribute to a determined detection of cognitive deficits and therefore to an improvement of diagnostics. Potentially, the results suggest strengthening the importance of relatives in the context of outpatient and inpatient care and research (ie, whenever a preferably functional and thorough detection of cognitive deficits is required).

CONCLUSIONS

Present data showed a considerable and relevant subjective impact of POCD on daily living functions, which was perceivable by both patients and relatives. In contrast to the self-assessment, long-term information on cognitive decline provided by relatives coincided more strongly with objective measurements, suggesting it to be a more reliable source. The findings of this study supported the significance of a combined internal and external assessment of cognitive deficits in the evaluation of POCD.

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4.7. Decreasing postoperative cognitive deficits after heart surgery: protocol for a randomized controlled trial on cognitive training (A7).[121]

Marius Butz, Jasmin El Shazly, Gebhard Sammer, Marlene Tschernatsch, Sabrina Kastaun, Mesut Yeniguen, Tobias Braun, Manfred Kaps, Andreas Böning, Ulrike Puvogel, Georg Bachmann, Thomas Mengden, Markus Schoenburg, Tibo Gerriets, Martin Juenemann

Das Auftreten postoperativer kognitiver Defizite, insbesondere nach Herzoperationen, wurde bereits in mehreren Studien nachgewiesen. Diese Defizite werden sowohl von den Patienten als auch ihren nahen Angehörigen im täglichen Leben deutlich wahrgenommen. Darüber hinaus können postoperative kognitive Defizite die Lebensqualität in Bezug auf die soziale Funktionsfähigkeit und die Erwerbsfähigkeit beeinträchtigen. Das Ziel dieser Studie ist es, zu untersuchen, ob ein frühes postoperatives kognitives Training subjektive und objektive postoperative kognitive Defizite reduzieren kann.

Bei diesem Vorhaben handelt es sich um eine multizentrische, zweiarmige, randomisierte, kontrollierte Studie mit 144 älteren Patienten, die sich einer elektiven Herzklappenoperation mit extrakorporaler Zirkulation unterziehen. Die Patienten werden entweder einer Trainingsgruppe oder einer Kontrollgruppe zugeteilt. Bei der Intervention handelt es sich um ein auf Papier und Bleistift basierendes kognitives Training, das für ca. eine halbe Stunde über einen Zeitraum von 18 Tagen durchgeführt wird. Das Training beginnt etwa 1 Woche nach der Operation und wird während der stationären Rehabilitationsphase durchgeführt. Die Kontrollgruppe erhält weder ein kognitives Training noch eine Placebo-Intervention. Eine detaillierte Beurteilung der psychologischen Funktionen und der gesundheitsbezogenen Lebensqualität vor der Operation bei der Entlassung aus der Rehabilitation und 3 und 12 Monate nach der Entlassung wird durchgeführt. Das primäre Ergebnis dieser Studie ist der Trainingseffekt auf die objektiven kognitiven Funktionen bei der Entlassung aus der Rehabilitation. Sekundäre Ergebnisse sind der Trainingseffekt auf die objektiven und subjektiven kognitiven Funktionen 3 und 12 Monate nach der Entlassung, das Auftreten einer Depression, die gesundheitsbezogene Lebensqualität und der Einfluss der perioperativen cerebralen Ischämie auf den Trainingseffekt. Ein perioperativ erlittener Hirninfarkt wird durch die Magnetresonanztomographie des Neurocraniums erfasst.

Sollte sich zeigen, dass dieses kognitive Training postoperative kognitive Defizite und die Lebensqualität verbessern kann, könnte diese Intervention im Rahmen eines multimodalen Therapieansatzes in die Frührehabilitation nach herzchirurgischen Eingriffen integriert werden.

Darüber hinaus hoffen wir, dass die Untersuchung der perioperativen Ischämie mittels diffusionsgewichteter Magnetresonanztomographie unser Verständnis der neurobiologischen Faktoren, die den Verlauf der postoperativen kognitiven Plastizität beeinflussen, verbessern wird.

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Trials

STUDY PROTOCOL Open Access

Decreasing postoperative cognitive deficits after heart surgery: protocol for a randomized controlled trial on cognitive training

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Abstract

Background: The occurrence of postoperative cognitive deficits, especially after heart surgery, has been demonstrated in several studies. These deficits can clearly be noticed by the patients and by their close relatives in daily life. Furthermore, postoperative cognitive deficits can decrease quality of life in social functioning and earning capacity. The aim of this study is to investigate whether early postoperative cognitive training can reduce subjective and objective postoperative cognitive deficits.

Methods: The proposed study is a multicenter, two-arm, randomized controlled trial involving 144 elderly patients undergoing elective heart-valve surgery with extracorporeal circulation. Patients will be assigned to either a training group or a control group. The intervention involves paper-and-pencil-based cognitive training, which is conducted for 36 min over a period of 18 days. The training starts about 1 week after surgery and is carried out during the hospitalized rehabilitation phase. The control group will not receive cognitive training or a placebo intervention. A detailed assessment of psychological functions and health-related quality of life prior to surgery at discharge from rehabilitation and 3 and 12 months after discharge will be performed. The primary outcome of this trial is the training effect on objective cognitive functions at discharge from rehabilitation. Secondary outcomes are the training effect on objective and subjective cognitive functions (3 and 12 months after discharge), depression, health-related quality of life, and the impact of perioperative cerebral ischemia on the training effect. Perioperative cerebral ischemia will be measured with postoperative magnetic resonance imaging including diffusion-weighted sequences.

Discussion: Should it be shown that our cognitive training can improve postoperative cognitive deficits and quality of life, one possibility could be to integrate this intervention into early rehabilitation. Furthermore, we hope that the investigation of perioperative ischemia by diffusion-weighted magnetic resonance imaging will improve our understanding of neurobiological factors influencing the course of postoperative cognitive plasticity.

(Continued on next page)

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(Continued from previous page)
Trial registration: German Clinical Trials Register (DRKS), DRKS00015512. Retrospectively registered on 21 September 2018.

Keywords: Heart surgery, Postoperative cognitive deficits, Postoperative cerebral microinfarcts, Magnetic resonance imaging, Cognitive training

Background

Neurological complications of cardiac surgery include ischemic and hemorrhagic stroke, seizures, delirium, cerebral hyperperfusion syndrome, cranial and peripheral nerve injuries, and postoperative cognitive decline (POCD) [1]. Amongst these, POCD seems to have the highest incidence, but its frequency strongly depends on the inclusion/exclusion criteria, the follow-up interval and the diagnostic criteria used [2]. There is no uniform definition of POCD, but a widespread criterion for POCD is a decline of 1 standard deviation from preoperative to 3 months postoperative in at least two objectively measured cognitive functions such as verbal memory, attention, cognitive flexibility, language, or visuomotor abilities [2]. Three months after coronary artery bypass grafting (CABG) surgery, POCD occurs in 16% [3] to 23% [4] of patients, and POCD has even been reported in 31% of patients 3 years after undergoing CABG [4]. A longitudinal study assessing the incidence of POCD in CABG surgery reported early improvement in cognitive function within 6 months after surgery that was followed by a later decline and led to a 42% incidence of POCD after 5 years. In this study, early POCD could be identified as an important predictor of long-term cognitive decline [5]. Even though POCD often appears as subclinical, both patients and their relatives report a significant decrease in patients' cognitive abilities in daily living up to at least 3 months after heart surgery [6]. In addition to POCD, postoperative cognitive improvement (POCI) is also reported, but its frequency seems to be 3–6 times lower than POCD [7].

Several perioperative conditions are discussed as potential pathophysiological mechanisms causing and promoting cerebral injury, such as global and regional hypoperfusion, pronounced temperature, arrhythmia, systemic inflammatory response, hemodilution, anesthesia itself and, particularly, cerebral (micro and macro) embolization followed by ischemia/reperfusion injury and subsequent blood-brain barrier dysfunction [8, 9]. A meta-analysis of randomized controlled trials has shown higher incidence of POCD in CABG with extracorporeal circulation (cardiopulmonary bypass, on-pump) compared to off-pump CABG 3 months after surgery [10]. In this respect, cerebral micro-embolization has been reported to substantially contribute to perioperative neurological complications [11].

Although the pathophysiology of POCD is still the subject of controversial debate, consequences of cognitive deficits are well-described. Aside from a decline in health-related quality of life (HQL) up to 5 years after surgery [12], POCD can result in reduced working and earning capacity with premature retirement, and diminished social functioning resulting in increased social dependency [13]. Cognitive abilities substantially contribute to personality and self-perception; in this light, daily perceived POCD can impose a profound and heavy burden on those concerned. For patients, relatives, and the healthcare system, it is of particular significance that POCD occurs during a highly vulnerable period of life, where cognitive deficits can quickly lead to loss of independence and thus increased need of long-term care [14].

Several studies have shown that patients with mild cognitive impairment (MCI) can benefit from computerized cognitive training [15]. These effects are mainly attributed to cognitive and neurological plasticity (i.e., the ability of the brain to alternate cognitive functions and structural or functional neurophysiological parameters through stimulation). In response to cognitive training, older healthy adults reproducibly present with an increased pattern in the gray and white matter structure [16]. Functional plasticity, on the other hand, shows a mixed pattern of increased and decreased activity in specific brain regions in older healthy adults and consistent increased activity in individuals with MCI, as a result of cognitive training [16]. Furthermore, a functional magnetic resonance imaging (MRI) study reported increased resting-state functional connectivity between the hippocampus and certain brain regions after effective cognitive training in patients with stroke [17]. Cognitive training is also associated with improvements in depression and everyday functioning [18]. To date, only one prospective investigation has addressed the value of cognitive training in patients undergoing cardiac surgery [19]. The authors reported a beneficial effect of memory and attentional training in patients who underwent CABG compared to patients who underwent CABG and received no additional cognitive training.

The purpose and primary outcome of this prospective, randomized and controlled study is to evaluate the effectiveness of a paper-and-pencil-based cognitive training program on objectively measured cognitive functions for patients undergoing cardiac surgery with

extracorporeal circulation. The primary outcome will be evaluated directly after training at discharge from rehabilitation. The delivery of the cognitive training will start at the beginning of rehabilitation, which means approximately 1 week after surgery. Secondary outcomes are the training effect on cognitive functions, depression and health-related quality of life 3 and 12 months after discharge from rehabilitation, and the impact of perioperative cerebral ischemia on the training effect. Perioperative cerebral ischemia will be measured with postoperative diffusion-weighted magnetic resonance imaging (DW-MRI) during the first postoperative week. To our knowledge, this is the first study to explore the impact of cerebral ischemia on cognitive training for patients who have undergone cardiac surgery.

Methods

Study design and enrollment

This study is a multicenter, randomized controlled trial conducted at the department of cardiac surgery of the Kerckhoff Heart and Thorax Center in Bad Nauheim, Germany, and at the department of cardiovascular surgery of the University Hospital Giessen, Germany. It complies with the Declaration of Helsinki and has been approved by the ethics committee of the Justus Liebig University Giessen (ref. 28/14). The study coordinator receives information about planned elective cardiac surgery from the participating study centers, which he screens according to eligibility criteria. Potential patients will be contacted and informed verbally and in writing in detail about the purpose, procedure, and possible consequences of the study project. If the patient agrees to participate, a written informed consent form will be signed by the patient and the investigator prior to the patient's enrollment.

Our study team consists of members of the departments of neurology, neuropsychology, neuroradiology, heart surgery, and rehabilitation who are responsible for running the study, including preparing the protocol, monitoring the study and writing the study reports. The study protocol follows the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) guideline (see Additional file 1).

Due to the planned small sample size, the expected lack of harm and the relatively short execution time of the cognitive training (3 weeks), the implementation of a data monitoring committee was not considered.

All patients will pass a detailed neuropsychological assessment the day before surgery, at discharge from rehabilitation, and at 3 and 12 months after discharge. At every time point, patients will complete a standardized questionnaire on depression and anxiety. Questions about cognitive failure in daily life and HQL will be assessed before heart surgery and at 3 and 12 months after discharge from rehabilitation. Before surgery, data documentation will include age, sex, education, body mass index, preexisting conditions, and medication. Documentation of perioperative date will be the type and amount of anesthesia administered, duration of anesthesia administration, type and amount of analgesia administered, duration of analgesia administration, duration of surgery, duration of extracorporeal circulation, cross-clamp time and perioperative complications. Post-surgery intensive care unit (ICU) days, total length of inpatient stay, postoperative complications and postoperative delirium will be recorded. At 6–10 days after surgery, MRI of the brain will be conducted to screen for cerebral ischemia, hemorrhage, or other acute pathologic conditions potentially confounding neuropsychological assessment and the effects of cognitive training. Following the inpatient stay in the acute hospital (approximately 7 days), patients will be directly transferred to the department of rehabilitation at the Kerckhoff Clinic in Bad Nauheim, Germany.

During their stay at the rehabilitation center, which usually lasts 3 weeks, all patients will receive standard cardiac rehabilitation including physical exercise, medical management and nutritional counseling. The cognitive training group will undergo an additional cognitive training program consisting of paper-and-pencil exercises. The study design is shown in Fig. 1. A detailed trial schedule in accordance with the Standard Protocol Items: Recommendation for Interventional Trials (SPIRIT) guideline is shown in Table 1.

Inclusion and exclusion criteria

Patients receiving elective aortic or mitral valve replacement/reconstruction with or without CABG will be included in this study. All heart operations will be performed with standard extracorporeal circulation. Due to the use of a standardized psychological assessment, patients must be native German speakers. Exclusion criteria are history of stroke and preexisting psychiatric or neurological disorders. Patients whose health insurance does not grant the postoperative treatment in the department of rehabilitation at the Kerckhoff Clinic in Bad Nauheim (Germany) must also be excluded.

If patients no longer wish to participate in the cognitive training or neuropsychological examination due to a deteriorating state of health, lack of motivation, any other reason, or without reasons given, they may discontinue participation in the study. Furthermore, participants will be excluded from the study if they are transferred to another clinic during their stay in the rehabilitation center.

Medical and psychological interventions in the context of other studies that may exert effects on patients' cognition are prohibited. In general, concomitant care and interventions as part of the standard rehabilitation program are permitted.

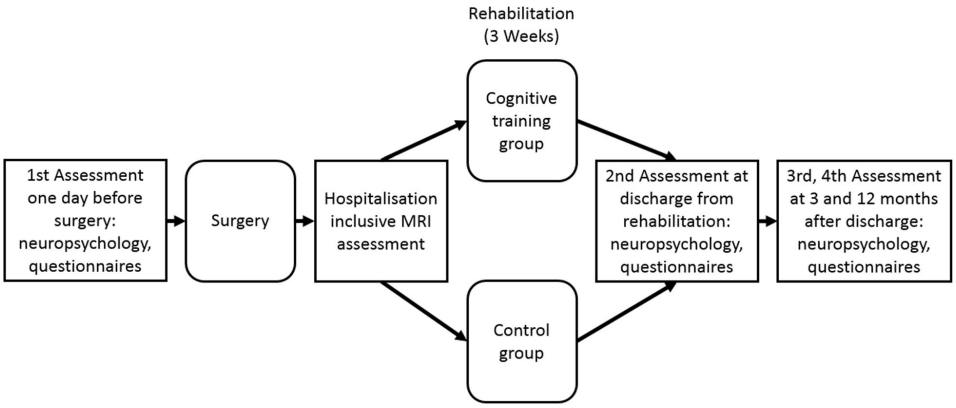

Fig. 1 Timeline of study-related events. The first assessment includes neuropsychological tests and questionnaires on the day before surgery. Within 6–10 days after surgery, magnetic resonance imaging (MRI) of the brain is scheduled. After the acute hospitalization, patients will be transferred to the center of rehabilitation and randomly assigned to the cognitive training group or the control group. A second neuropsychological assessment will be administered at discharge from rehabilitation. To determine the long-term effects of the cognitive training, a neuropsychological test and questionnaires will be administered at 3 and 12 months after discharge from rehabilitation

Randomization

After enrollment and a baseline assessment, patients will randomly be assigned by the study coordinator to the cognitive training group or the control group, which will not receive cognitive training. Patients will be randomized using a computer-generated randomization list with a 1:1 blocked allocation ratio. The randomization list will be sequentially numbered and will be generated by the study coordinator prior to the start of the study.

Blinding

Surgeons, radiologists and neuropsychologists who are involved in the outcome variables will be blinded to the randomization status. Cognitive testing and training will be carried out by two different, experienced neuropsychologists in order to maintain the blinding. During follow-up assessments, patients may tell the blinded neuropsychologist accidentally before the start of the neuropsychological test whether or not they have received previous cognitive training. In this case, however, the neuropsychological test will be performed and discussed in the study reports.

Neuropsychological assessment

A battery of cognitive tests will be performed by a neuropsychologist on the day before surgery, at discharge from rehabilitation, and at 3 and 12 months after discharge. When available, parallel test forms will be used at follow up to account for learning effects. The order in which the parallel test forms are presented will be counterbalanced so that each parallel test form occurs with the same frequency at each test time point.

The cognitive test battery assesses selective attention, verbal and visual memory with short-delay and long-delay episodic memory conditions, verbal working memory, cognitive flexibility, word fluency and symbol processing. Selective attention will be examined using the Trail Making Test A (TMT-A) [20] and the *Alterskonzentrationstest* (AKT) [21]. In the TMT-A, the patient has to link numbers in ascending order on a test sheet. The AKT consists of a matrix of similar visual stimuli, where a target stimulus has to be marked.

To assess verbal memory, the *Verbaler Lern- und Merkfähigkeitstest* (VLMT), a modified German version of the Rey Auditory Verbal Learning Test [22], will be applied. This test can be used to evaluate short-term memory, learning, episodic memory, and verbal discriminability. First, the patient has to concentrate on a word list that is read out loud by the investigator. The direct retrieval of the patient is scored as short-term memory performance. Second, the patient has to learn the word list in five learning trials. The sum of the recalled words represents a learning parameter. Third, a second word list with new words is presented verbally only once, to divert attention from the first word list. After this, the learned words of the first word list have to be recalled; this is used as a measurement of a short-delayed function of verbal episodic memory. A second verbal episodic memory measurement is performed 20 min later (long delay). Finally, the verbal recognition ability is proven by discriminating between already learned and

Table 1 Trial schedule of enrollment, interventions, and assessments

STUDY PERIOD							
	Enrolment	**Post-allocation**					**Close-out**
TIME POINT	$-t_1$	t_1	t_2	t_3	t_4	t_{3m}	t_{12m}
ENROLMENT:							
Eligibility screen	X						
Informed consent	X						
Allocation	X						
INTERVENTIONS:							
Heart surgery		X					
Cognitive training				←	→		
ASSESSMENTS:							
MRI			X				
TMT	X				X	X	X
AKT	X				X	X	X
VLMT	X				X	X	X
Block tapping	X				X	X	X
NVLT	X				X	X	X
SKT	X				X	X	X
RWT	X				X	X	X
SVT	X				X	X	X
HADS	X				X	X	X
s-CFQ	X					X	X
f-CFQ	X					X	X
SF36	X					X	X

MRI magnetic resonance imaging, *TMT* Trail Making Test, *AKT Alterskonzentrationstest*, *VLMT Verbaler Lern- und Merkfähigkeitstest*, *NVLT* Non-Verbal Learning Test, *SKT Syndrom-Kurztest*, *RWT Regensburger Wortflüssigkeits-Test*, *SVT Symbolverarbeitungstest*, *HADS* Hospital Anxiety and Depression Scale, *s-CFQ* Cognitive Failure Questionnaire for self-assessment, *f-CFQ* Cognitive Failure Questionnaire for foreign assessment, *SF36* Short Form-36

new words. Between the short-delayed verbal episodic memory trial and the long-delayed verbal episodic memory trial, nonverbal cognitive tests are performed to avoid the potential effect of interfering words not included in the learned wordlist.

Visual memory will be examined using the Block-Tapping Test [23], the Non-Verbal Learning Test (NVLT) [24] and the pictorial memory subtest of the German *Syndrom-Kurztest* (SKT) [25]. In the Block-Tapping Test, the patient has to tap blocks on a board with his or her hand in a given order forward and backward. The NVLT is a test to evaluate the visual recognition of repeated abstract symbols within a variety of 60 cards. The pictorial memory subtest of the German SKT will be administered to the patient to evaluate short-term episodic memory and recognition of 12 visual pictures, which are presented in one learning trial. With the Letter Number Test, a subtest of the MATRIX test

battery, the verbal working memory is tested through the mental reorganization of numbers and letters [26]. Cognitive flexibility will be assessed by the Trail Making Test B (TMT-B) [20], where numbers and letters have to be alternately linked, and by another subtest of the SKT (SKT 7) [25], where the patient has to name interfering letters (e.g., "A" instead of "B," and vice versa).

Furthermore, semantic and phonetic verbal fluency will be tested using the "Regensburger Wortflüssigkeits-Test" (RWT) [27]. In this test, in 1 min, the patient has to name words from a specific category to test semantic fluency and words with a specific initial letter to test phonetic fluency. At the end of the test battery, the *Symbolverarbeitungstest* (SVT) will be performed to test the processing of symbolic pictures [28].

Questionnaires

Study patients will complete a validated German version of the Cognitive Failures Questionnaire for self-assessment (s-CFQ) [29]. Close relatives of the patients will answer a cognitive questionnaire to evaluate foreign assessment (f-CFQ) [30]. The questionnaires will examine the frequency of failures in daily living related to memory, attention, action, and perception. Because memory impairment is an important element that affects everyday functioning, the s-CFQ was modified with additional questions related to memory failures, taken from the validated German version of the Memory Complaint Questionnaire [31]. Depression and anxiety will be scored using the validated German version of the Hospital Anxiety and Depression Scale (HADS) [32]. HQL will be assessed using the Short Form-36 (SF36) questionnaire [33]. The SF36 covers eight health-related factors including vitality, physical functioning, bodily pain, general health perceptions, physical role functioning, emotional role functioning, social role functioning, and mental health. The HADS will be used at every neuropsychological test time point; the s-CFQ, f-CFQ and SF36 will be completed at baseline and 3 and 12 months after discharge from rehabilitation.

Magnetic resonance imaging

Cranial MRI will be performed 6–10 days after surgery using a 3-T scanner (Skyra; Siemens, Erlangen, Germany). The protocol of imaging will include a T2-weighted turbo spin-echo sequence (slice thickness = 3 mm, field of view (FOV) = 220 × 220 mm, matrix = 512 × 391, repetition time (TR) = 7490 ms, echo time (TE) = 100 ms), a T2-weighted turbo spin-echo sequence for dark fluid (slice thickness = 3 mm, FOV = 220 × 220 mm, matrix = 320 × 224, TR = 7000 ms, TE = 81 ms), a T1-weighted FLASH sequence (slice thickness = 3 mm, FOV = 220 × 220 mm, matrix = 320 × 320, TR = 250 ms, TE = 2.49 ms) and a diffusion-weighted echo-planar imaging sequence (slice thickness = 3 mm, FOV = 220 × 220 mm, matrix = 160 × 160, TR = 7720 ms, TE = 64 ms, slice gradients of b values = 0 and 1000 s/mm^2). The postoperative diffusion-weighted sequence will be used by two blinded, experienced observers for registration and planimetric evaluation of acute ischemic lesions.

Primary outcome measure

The primary outcome measure will be the training effect on all objectively measured neuropsychological functions at discharge from rehabilitation.

Secondary outcome measure

As a secondary outcome, we will evaluate the training effect of all objectively measured neuropsychological functions at 3 and 12 months after discharge from rehabilitation. Second, we will evaluate the training effect on the subjective self-assessment and external assessment by relatives of cognitive failures at 3 and 12 months after discharge from rehabilitation. Third, we will evaluate the training effect on HRQ at 3 and 12 months after discharge from rehabilitation. Fourth, we want to investigate the extent to which the cognitive training has an impact on depression at all follow-up time points. Last, we will examine the impact of perioperative cerebral ischemia on the neuropsychological measured training effect at all follow-up time points. Perioperative cerebral ischemia will be measured with postoperative DW-MRI during the first postoperative week. The number and size of ischemic lesions are determined and will be used as a control variable for the analysis of the training effect.

Cognitive training

There is currently only one study in which effective cognitive training was performed in patients undergoing cardiac surgery [19]. This study used a combination of computer-based training (with a focus on selective attention) and memory strategy training (method of loci). We decided against this training concept because we think that our elderly patients are not familiar with the use of computers, and we will therefore use a purely paper-and-pencil approach. Second, memory strategies seem to be less effective than cognitive exercises such as computerized or paper-and-pencil procedures [34]. To our knowledge, there is no specific cognitive domain that clearly emerges over time in the context of POCD, such as memory or attention. Therefore, we decided to train several cognitive functions that are used especially in everyday life to maintain social functions and earning capacity. These include word fluency, working memory, attention, and the ability to plan.

For the preparation of our training program we first conducted a literature search on German-language-validated

paper-and-pencil-based cognitive exercise methods. The literature is very scarce. In a controlled study design, a training program by Müller et al. (2004) [35] showed cognitive improvements in patients with executive dysfunction [36]. Their program included training in word fluency, cognitive flexibility, working memory, and planning ability. However, we found the cognitive training of Müller et al. (2004) [35] in some parts to be too unentertaining for our patients, whereby we took over only a few training tasks and combined them with new tasks designed by our group to achieve better acceptance.

Cognitive training in the intervention group will include paper-and-pencil-based exercises practicing multi-domain cognitive executive functions such as word fluency, verbal and visual working memory, selective visual attention, and planning. One training session will last approximately 40 min and will be performed 6 days a week for 3 weeks.

The daily training program consists of eight different types of standardized tasks addressing the processing of words, categories, images, head calculation, and planning. New words, categories, images, head calculations, and planning tasks will be presented on each training day. Each task takes between 2 and 10 min; to manage the working time, the patients must limit their work using a digital clock. At the beginning of the training program, a trained investigator will give explicit instructions in a one-to-one training session and will be nearby to help with any questions about the exercises. If no further help is needed in the following training days, the patient will be provided with training material for the following 6 days so that patients can complete the training independently in their ward rooms. Each task contains precise written instructions that can be used to assist in its execution. If a patient has questions about the training, he or she can contact the trainer. After every 6th day, the extent to which the tasks have been completed is checked by the training investigator and new training material will be provided. Patients are told that their exercise solutions are not evaluated or corrected. Therefore, it does not matter whether the solutions are right or wrong. An important concern for the patients is that they concentrate on the tasks and cognitively exert themselves. In this way, we can avoid possible performance pressure and also avoid patients exchanging the right approaches among themselves. The different types of tasks are presented in the following standardized order.

Phonetic word fluency

The patient is given three letters on a sheet of paper. Within 2 min, he or she has to note as many words as possible that begin with these letters. This task is mainly intended to train word fluency and was adapted from Müller et al. (2004) [35].

Categorical word fluency

In this task, the patient is given three different categorical terms on a sheet of paper. Within 2 min, as many words as possible that can be assigned to these categories must be found and noted. This task is mainly intended to train word fluency and was adapted from Müller et al. (2004) [35].

Comic strips

Patients receive 4–5 popular German comics from German illustrators such as Wilhelm Busch, Erich Ochser or Hans Jürgen Press, with 3–16 pictures of a story in mixed order. Within 5 min, the pictures have to be arranged mentally in a meaningful order. The new invented order should be documented by numbering the pictures with a pencil. This task is mainly intended to train working memory and was created by our group.

Mental arithmetic

The patient is asked to complete several calculation tasks on a sheet of paper. The result of the first arithmetic problem, which includes addition, subtraction and multiplication of numbers, must be memorized. In the second step, another calculation task must be solved, and the result must also be memorized. In the last step, the last result should be subtracted from the first result, and the final result should be written down. The time limit for this exercise is 5 min. This task is mainly intended to train working memory and was adapted from Müller et al. (2004) [35].

Synonymic fluency

The next worksheet contains three different terms. For each term, patients must find words with similar meanings (synonyms). For example, if the term is *wallet*, then other words would be *portmonee* or *money purse*. The time limit is 2 min. This task is mainly intended to train word fluency and was created by our group.

Fill in the blank text

In the next training task, short stories are presented. These are generally known stories by Wilhelm Busch, the Brothers Grimm, Hans Christian Andersen or fables from antiquity, German studies, Buddhism, and Japan. The stories have gaps that have to be filled in with a self-chosen, meaningful word. The time limit for this exercise is 5 min. This task is mainly intended to train word fluency and working memory and was constructed by our group.

Where is Waldo

An illustration of Martin Handford's "Where is Waldo?" is presented on a DIN A3 sheet of paper. The picture contains dozens or more people doing a variety of things

in a particular place. The patient has to find some specific signs or objects listed on a sheet of paper by marking them with a pen on the DIN A3 sheet within 5 min. This task is mainly intended to train selective attention and working memory and was created by our group.

Planning

In the last task, the patient must read a text in which an imaginary person has to perform transactions or organize appointments. The patient's task is to solve the problems by writing down a concrete solution. The time limit for this task is 10 min. The task is mainly intended to train planning ability and working memory and was adapted from Müller et al. (2013) [37].

Planned statistical analyses

The effect of cognitive training will be analyzed by repeated measures (mixed between-within) analysis of variance (ANOVA) with groups (control group/intervention group) as the between-subject factor and assessment time (baseline and all follow-up assessments) as the within-subject factor for all cognitive tests and questionnaires, respectively. Assumptions for repeated measures ANOVA will be tested using the Levene test for variance-homogeneity and Mauchly's test for sphericity. If sphericity is violated, alpha levels will be adjusted using the Greenhouse-Geisser correction. Normal distribution will be tested using the Shapiro-Wilk test. To control for the possibility of confounder variables that could affect the results, we will conduct additional repeated measures analysis of covariance (ANCOVA), which includes covariates such as preoperative cognitive values, age, sex, education, psychiatric scores (depression/anxiety), and perioperative variables such as duration of extracorporeal circulation, administration of anesthesia, and number and size of ischemic lesions.

Post hoc explorative between-subject comparisons will be analyzed using the t test for independent samples. In this case, we will compare the intervention group with the control group by calculating a change score in cognitive values (post-training score minus pre-training score). The change in cognitive values is the dependent variable, and the treatment group (cognitive training group/control group) is the independent variable.

Within-subject comparisons will be analyzed using the paired t test. When the assumptions for parametric tests (normal distribution, variance-homogeneity between two groups) are not given, the variables will be analyzed using non-parametric variance techniques. In this case, between-group differences will be calculated using the Mann-Whitney U test, using change scores in cognitive values (post-training score minus pre-training score) and the Wilcoxon signed-rank test for within-group comparisons. Nominal variables will be analyzed by Pearson's chi-squared test. Depending on the parametric level of the data, correlation with continuous variables will be calculated using Pearson product-moment correlation, Spearman rank correlation, or Kendall tau correlation. Effect size of the cognitive training will be calculated by the difference in the pretest-posttest measure between the intervention and control group, weighted by the pooled standard deviation of the pretest measurement, because this is the recommended choice for a pretest-posttest controlled design [38]. The criterion for statistical significance will be set at $p < 0.05$. In the case of multiple tests, we will control p values using the false discovery rate (FDR) correction method [39]. Since we expect dropout of some patients on follow-up assessments, all patients will be included in the intention-to-treat analysis, where missing data will be imputed by a multiple imputation method. To evaluate the impact of missing data, a complete case analysis will also be performed, followed by best-worst and worst-best case sensitivity analyses.

Another approach to identifying a training effect on cognition will be to compare the frequencies of POCD and POCI between the groups using Pearson's chi-squared test. POCD will be defined as a decline from pre to post assessment of 1 standard deviation in at least two neuropsychological parameters as this is a widely used method [2]. Similarly, POCI will be defined as an improvement from pre to post assessment of 1 standard deviation in at least two neuropsychological parameters.

Interim analyses will be carried out during the study period to identify adverse events, an overwhelming effect, or the futility of the experimental arm. In this case, the study could be terminated prior to its completion. The decision will be made by the study team.

Power and sample size estimation

Cognitive training for patients undergoing heart surgery administered by de Tournay-Jette et al. (2012) [19] revealed medium-to-large effect sizes ($\eta^2 = 0.10–0.23$). We have decided to use the smaller effect size ($\eta^2 = 0.10$) for calculation so as not to underestimate the required sample size. Using this effect size, 37 patients per group are needed to obtain statistical power of 80% at a significance level of $p = 0.05$ (two-tailed). Based on previous cardiosurgical studies, we estimate a dropout rate of 20% between each of the four assessment time points. Thus, the number of study patients recruited at baseline assessment was fixed at 72 patients per group. For sample size and statistical power calculations, we used G*Power-3 analysis software.

Data management

All personal information about enrolled patients will be subject to medical confidentiality. Paper-based assessment

forms will be used to record the outcome variables. The data will be manually entered in an electronic database, which is password-protected and will be checked for quality and accuracy. All assessment forms, signed informed consent forms, and the randomization list will be stored in a locked cabinet.

Dissemination policy

Our goal is to make the study results available to the general public, healthcare providers, and scientists by publishing them in the public press, at scientific congresses, and as original articles in peer-reviewed journals. The results will be reported regardless of the amount and direction of the effect.

Discussion

The aim of this study is to evaluate a paper-and-pencil-based cognitive training program for patients undergoing heart surgery with extracorporeal circulation. POCD shows the highest incidence of neurological complications that can occur in the context of surgery, especially cardiac surgery [1]. Adverse effects of POCD on daily living abilities can be noticed by patients themselves and their relatives in both the short and long term [6]. The etiology remains controversial but can be considered a multifactorial event in which extracorporeal circulation plays a crucial role [8].

Here, we present cognitive training that integrates well with standard rehabilitation, takes place as early as possible, and aims to reduce the occurrence and persistence of cognitive deficits in the short and long term. It is also of interest whether patients with perioperative ischemic stroke benefit from this intervention to varying degrees or in different forms.

We intentionally opted for technically simple paper-and-pencil-based training tasks because POCD after cardiosurgical procedures mainly affects elderly people. Many studies on the effect of cognitive training have used computer-based training tasks [15], which provide the advantage of generating and capturing data simply, quickly and very precisely. However, even today, they often represent an unfamiliar medium for older people, which could lead to irritation, fear of contact, and/or frustration in the older population studied here and thus constitute a potential bias. A placebo intervention for the control group is intentionally omitted because cognitive effects of placebo interventions on cognitive performance are difficult to control. In order to credibly suggest to patients that the placebo intervention could have an influence on their memory and thus also to achieve a willingness to participate, the structure of the placebo intervention will have to be closely related to cognitive training (e.g., relaxation exercises, crossword puzzles, conversation therapy, computer games, etc.) and thus also achieve cognitive training effects.

The only prospective investigation of patients undergoing cardiac surgery to date reported a beneficial effect of memory and attentional training in patients who underwent CABG [19], but no information was given on the use of extracorporeal circulation in this collective. In this study, training took place between the 6th and the 10th week following surgery. However, it is still not clear when the optimal time point for cognitive training should be set and for how long the intervention should be carried out. It seems possible that the rehabilitation of postoperatively impaired cognitive function will be more improved by an earlier intervention starting in the range of a week compared to one month after surgery. Controlled studies on neurorehabilitation of post-stroke cognitive impairment have shown beneficial effects for several cognitive functions when restitutive cognitive training begins within 2 weeks [40] or about 7 months [17] after stroke onset. Animal models suggest a time-dependent increase in neuroplasticity (plastic window) after ischemic injury, with a peak at 7–14 days and near completion at 30 days. Nevertheless, it should be noted that the assignability of these findings from bench to bedside is difficult, and the shape and extent of the neuroplastic window in humans remains unclear [41].

In our study, the detection of acute, perioperative cerebral ischemia is performed by MRI with DWI. With the use of DWI, a preoperative baseline assessment is not necessary because in this sequence, acute ischemic tissue is presented as a bright area that typically occurs 2–3 h after the onset of damage and usually subsides within 2–3 weeks [42]. These acute cerebral ischemic lesions can be detected by DW-MRI in 14–61% of the patients after cardiac surgery [11, 43]. The significance of those acute MRI lesions, especially with regard to manifestation of POCD, remains unclear [42]. To our knowledge, there are no studies controlling for the potentially confounding effect of peri-interventionally endured cerebral ischemia detected during the first postoperative week. In this context, it seems of particular interest whether patients with acute cerebral ischemia benefit from cognitive training to any other degree or in any other form.

So far, increased efforts have been made to prevent POCD, addressing anesthesia, cardiotechnology, and cardiac surgery [9], with limited but measurable success; these procedural preventive measures alone can reduce the incidence of POCD in the magnitude of 30% [44]. In contrast to procedural prevention strategies, the concept of cognitive training allows the

patient to act independently, responsibly and actively. This can perhaps exert a positive effect on the recovery process through the experienced self-efficacy that seems to contribute to better recovery after heart surgery in terms of patients' worries, energetic mood, reading, ambulating, and fitness [45]. With the knowledge that cognitive deficits can be actively addressed afterward, the fear of surgery can possibly be reduced; finally, one must not forget the drastic experience of a potentially life-threatening cardiac disease. Preoperative anxiety has been shown to be a predictor of major morbidity and mortality in patients who have undergone heart surgery [46].

The present investigation certainly contains some limitations. First of all, participation in the study is tied to the performance of a heart operation using a heart-lung machine. A comparison with patients undergoing off-pump cardiac surgery is therefore not possible. Given the lack of knowledge about the optimal starting time or duration of training, the intervention may be too early or the duration of approximately 3 weeks too short. It could also be discussed as to whether an additional follow-up investigation after several years would provide further valuable information on the long-term course of POCD and the training effects. For the aforementioned reasons, no placebo intervention is planned in the present study; this may formally affect the quality of the study and the transferability of the results. Finally, our cognitive training consists of a combination of validated [36] and unvalidated tasks. Since our self-created tasks are not validated, we do not know whether they might potentially contribute to an alteration in cognition.

The results of our study could have potentially important implications for the prevention and treatment of POCD. In particular, if our cognitive training is feasible and effective in maintaining or improving cognition and quality of life, it could be integrated into the treatment programs of rehabilitation centers that treat patients after heart surgery. Economically and organizationally, this is possible without much effort because the cognitive exercises are independently workable and need no great control, and rehabilitative centers usually have psychologists who could be involved in the organization of the exercises, distribution of tasks, or clarification of questions. Furthermore, the cognitive training is designed in such a way that it could also be carried out in an ambulant setting.

Trial status

The study is currently enrolling patients. Recruitment started on 13 July 2016. Recruitment is expected to be completed in February 2020. Protocol version: 1.4 (10-08-2019).

Supplementary information

Supplementary information accompanies this paper at https://doi.org/10.1186/s13063-019-3799-0.

Additional file 1. SPIRIT 2013 Checklist: recommended items to address in a clinical trial protocol and related documents.

Abbreviations

AKT: Alterskonzentrationstest; ANCOVA: Analysis of covariance; ANOVA: Analysis of variance; CABG: Coronary artery bypass grafting; DW-MRI: Diffusion-weighted magnetic resonance imaging; FA: Fractional anisotropy; f-CFQ: Cognitive Failure Questionnaire for foreign assessment; FDR: False discovery rate; FOV: Field of view; HADS: Hospital Anxiety and Depression Scale; HQL: Health-related quality of life; ICU: Intensive care unit; MCI: Mild cognitive impairment; MRI: Magnetic resonance imaging; NVLT: Non-Verbal Learning Test; POCD: Postoperative cognitive decline; POCI: Postoperative cognitive improvement; RWT: Regensburger Wortflüssigkeits-Test; s-CFQ: Cognitive Failure Questionnaire for self-assessment; SKT: Syndrom-Kurztest; SVT: Symbolverarbeitungstest; TE: Echo time; TMT: Trail Making Test; TR: Repetition time; VLMT: Verbaler Lern- und Merkfähigkeitstest

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None.

Authors' contributions

MB: conception and design (study protocol, neuropsychological assessment, cognitive training), patient recruitment, collection of neuropsychological and medical data, data analysis, data interpretation, manuscript writing, and critical revision. JES: conception and design (study protocol, neuropsychological assessment, cognitive training), patient recruitment, collection of neuropsychological and medical data, data analysis, data interpretation, and critical revision. GS: conception and design (study protocol, neuropsychological assessment, cognitive training), data analysis, data interpretation, and critical revision. MT: critical revision. SK: conception and design (study protocol) and critical revision. MY: critical revision. TB: critical revision. MK: critical revision. AB: responsible for surgical process and critical revision. UP: collection of medical data and critical revision. GB: conception and design (study protocol), collection of MRI data, and critical revision. TM: conception and design (study protocol), responsible for medical rehabilitation, and critical revision. MS: conception and design (study protocol), responsible for surgical process and critical revision. TG: conception and design (study protocol), data interpretation, and critical revision. MJ: conception and design (study protocol), data interpretation, manuscript writing, and critical revision. All authors read and approved the final manuscript.

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Availability of data and materials

The datasets analyzed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

Central ethical approval has been confirmed from the Justus Liebig University Giessen (ref approval no. 28/14) and we will not begin recruiting at other centers in the trial until local ethical approval has been obtained. All amendments to the protocol will be submitted to the ethics committee of the Justus Liebig University Giessen. Each patient will give written informed consent. The written informed consent form is available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Publisher's Note

4.8. Neuroprotective mechanisms of erythropoietin in a rat stroke model (A8).[122]

Martin Juenemann, Tobias Braun, Nadine Schleicher, Mesut Yeniguen, Patrick Schramm, Tibo Gerriets, Nouha Ritschel, Georg Bachmann, Martin Obert, Markus Schoenburg, Manfred Kaps, Marlene Tschernatsch

Im Rahmen der zunehmenden Durchführung elektiver kardiovaskulärer Eingriffe sind vielfach hirnschädigende Komplikationen vorbeschrieben; diese Situation bietet jedoch auch die Möglichkeit, präventive neuroprotektive Maßnahmen zu ergreifen. Diese Studie wurde konzipiert, um die indirekten neuroprotektiven Eigenschaften der Vorbehandlung mit rekombinantem humanem Erythropoietin (rhEPO) in einem Rattenmodell des transienten Verschlusses der A. cerebri media (middle cerebral artery occlusion, MCAO) zu untersuchen.

110 männliche Wistar-Ratten wurden randomisiert vier Gruppen zugeordnet, die 15 Minuten vor dem MCAO entweder 5.000 IE/kg rhEPO intravenös oder Kochsalzlösung sowie eine bilaterale Kraniektomie oder Scheinkraniektomie erhielten. Die bilaterale Kraniektomie zielte auf die Beseitigung des raumfordernden Effekts eines postischämischen Ödems ab. Das diagnostische Programm umfasste eine neurologische Untersuchung, die Beurteilung der Infarktgröße und des Hirnödems mittels Magnetresonanztomographie, die Nass-Trocken-Technik und eine Quantifizierung des hemisphärischen und lokalen cerebralen Blutflusses (CBF) mittels Flachdetektor-Computertomographie.

In Abwesenheit einer Kraniektomie führte die EPO-Vorbehandlung zu einer signifikanten Reduktion des Infarktvolumens (34,83 ± 9,84% vs. 25,28 ± 7,03%; p = 0,022) und der Mittellinienverschiebung (0,114 ± 0,023 cm vs. 0,083 ± 0,027 cm; p = 0,013). Wir beobachteten eine signifikante Zunahme des regionalen CBF in kortikalen Bereichen des ischämischen Infarkts (72,29 ± 24,00% vs. 105,53 ± 33,10%; p = 0,043), aber nicht in den gesamten Hemisphären. Infarktgrößenunabhängige Parameter konnten keine statistisch signifikante Reduktion des Hirnödems unter EPO-Behandlung nachweisen.

Die einmalige Vorbehandlung mit rhEPO 5.000 IU/kg reduziert das ischämische Läsionsvolumen signifikant und erhöht den lokalen CBF in penumbralen Bereichen der Ischämie 24 h nach transientem MCAO bei Ratten. Die Ergebnisse deuten auf eine Erythropoietin-vermittelte, indirekte Neuroprotektion durch eine Ödemreduktion und die daraus resultierenden drucksenkenden und blutflusssteigernden Effekte hin.

Research Article

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Neuroprotective mechanisms of erythropoietin in a rat stroke model

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Abstract

Objective – This study was designed to investigate the indirect neuroprotective properties of recombinant human erythropoietin (rhEPO) pretreatment in a rat model of transient middle cerebral artery occlusion (MCAO).

Methods – One hundred and ten male Wistar rats were randomly assigned to four groups receiving either 5,000 IU/kg rhEPO intravenously or saline 15 minutes prior to MCAO and bilateral craniectomy or sham craniectomy. Bilateral craniectomy aimed at elimination of the space-consuming effect of postischemic edema. Diagnostic workup included neurological examination, assessment of infarct size and cerebral edema by magnetic resonance imaging, wet–dry technique, and quantification of hemispheric and local cerebral blood flow (CBF) by flat-panel volumetric computed tomography.

Results – In the absence of craniectomy, EPO pretreatment led to a significant reduction in infarct volume (34.83 ± 9.84% vs. 25.28 ± 7.03%; $p = 0.022$) and midline shift (0.114 ± 0.023 cm vs. 0.083 ± 0.027 cm; $p = 0.013$). We observed a significant increase in regional CBF in cortical areas of the ischemic infarct (72.29 ± 24.00% vs. 105.53 ± 33.10%; $p = 0.043$) but not the whole hemispheres. Infarct size-independent parameters could not demonstrate a statistically significant reduction in cerebral edema with EPO treatment.

Conclusions – Single-dose pretreatment with rhEPO 5,000 IU/kg significantly reduces ischemic lesion volume and increases local CBF in penumbral areas of ischemia 24 h after transient MCAO in rats. Data suggest indirect neuroprotection from edema and the resultant pressure-reducing and blood flow-increasing effects mediated by EPO.

Keywords: neuroprotection, rat, recombinant human erythropoietin, transient focal cerebral ischemia, vascular disorders, craniectomy

1 Introduction

To date, many studies have been conducted on the identification, development, and evaluation of pharmacological neuroprotectants. In this context, experimental

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research has demonstrated that systemically administered recombinant human erythropoietin (rhEPO) partially crosses the blood–brain barrier (BBB) with a latency and is able to reduce neuronal damage in animal models of cerebrovascular, neuroinflammatory, and neurodegenerative diseases as well as traumatic central nervous system (CNS) injury [1–4]. Depending on the study design, preclinical studies on EPO in stroke models indicate an improvement in infarct size by up to 32% and neurobehavioral outcomes by almost 40% [5,6].

Erythropoietin production in the CNS seems to be triggered by hypoxia. Astrocytes, as well as oligodendrocytes, endothelial cells, neurons, and microglia, endogenously produce EPO. In principle, several types of EpoR receptors exist, including the homodimeric receptor $(EpoR)_2$, a soluble as well as a heterodimeric receptor comprising a functional interaction of EpoR with the common β receptor (βcR, also known as CD131). The homodimeric EpoR has been detected on neural progenitor cells (NPCs), neurons, astrocytes, endothelial cells, and microglia [7–9]. Upregulation of EPO and EpoR in infarct and peri-infarct regions has been demonstrated in the course of focal cerebral ischemia/hypoxia [10]. The interaction of EPO and its receptor induces the phosphorylation of Janus kinase 2, which leads to the activation of phosphoinositide 3-kinase–serine–threonine kinase Akt and/or the signal transducer and activator of transcription 5 and/or the nuclear factor-κB pathway [11]. In this system, the EPO may exert neuroprotective effects via antiapoptotic mechanisms, stimulation of NPC proliferation and differentiation, neurogenesis, angiogenesis, and modification of inflammatory response and also induces erythropoiesis [7,8,12]. The heterodimeric EpoR/βcR receptor has been detected in various EPO-responsive tissues, including the cells of the CNS, such as microglia, and of the heart and kidney. It has been shown that this coexpression mediates the tissue-protective properties of EPO rather than erythropoietic effects [13].

Neuroprotection consists of prevention and opposition of pathological neuronal loss in diseases of the CNS [14]. Within cerebral ischemia, this loss can only partly be attributed to vessel occlusion. Moreover, perfusion deficits and the adjacent functional decline following cerebral vessel occlusion are consequences of the space-occupying effect of postischemic cerebral edema. Experimental data suggest that tissue swelling due to vasogenic edema during the hyperacute phase (<6 h) of stroke has considerable influence on temporospatial progression of the ischemic area by compromising microcirculation within critically perfused tissue at risk [15–18]. Therapeutic measures aiming at reducing cerebral edema and its space-occupying effect in the early stages of stroke may therefore induce an indirect "secondary" neuroprotection [16].

Most experimental studies focused on EPO treatment within the first hours following vessel occlusion [7], simulating the unpredictable situation clinicians face in the emergency department or in the stroke unit after sudden onset of a neurological deficit. However, with the advent of interventions in the cardio- and cerebrovascular systems – such as carotid endarterectomy and stenting, coronary artery bypass grafting, percutaneous coronary and cerebrovascular thrombectomy, angioplasty or coiling, and clipping of cerebral aneurysms – that carry an increased risk of stroke or require transient cerebral artery occlusion [19–26], anticipatory neuroprotection preceding a risk-related procedure demands greater attention [27]. In this context, experiments on a rodent model for transient middle cerebral artery occlusion (MCAO) suggest that beneficial effects of EPO treatment before ischemia onset can have a definite (if indirect) impact on the extent of ischemic edema and preservation of BBB function [27].

This study was designed to investigate secondary neuroprotective properties of rhEPO treatment preceding transient MCAO in a rodent stroke model. Dosage (5,000 IU/kg) and intravenous application were chosen according to the findings from the corresponding in vivo studies, considering the significantly low BBB permeability of this compound [1,7,28]. The multimodal approach included magnetic resonance imaging (MRI), flat-panel volumetric computed tomography (fpVCT), and quantification of brain water content (BWC) by the wet–dry technique. Elimination of the space-occupying effect of cerebral edema was achieved by bilateral craniectomy [29].

2 Methods

2.1 Animal preparation and surgical procedures

Male Wistar Unilever rats (HsdCpb:WU; Harlan Winkelmann, Germany) with a mean body weight of 310 g (±19.47 g) were used. Prior to surgery, each rat was administered 100 mg/kg metamizole (Novalgin®; Sanofi, Germany) orally. Anesthesia was established with 5% isoflurane delivered in air at 3.0 L/min and maintained

during surgery via a facial mask with 2–3% isoflurane delivered in air at 0.5 L/min. The core body temperature was recorded with a feedback-controlled heating pad and kept at 37.0°C (±0.25°C) during surgery and imaging procedures.

In addition to considerable neurological deficits, rodents often exhibit pronounced cardiorespiratory instability after occlusion of the middle cerebral artery (MCA). Since this study was not intended to evaluate the craniectomy itself, but rather the effect of EPO under various pressure conditions, the craniectomy was performed before MCAO to avoid provoking an increased dropout rate through additional anesthesia and intervention with an already potentially unstable animal. Bilateral or sham craniectomies were performed after local anesthesia (2% lidocaine; Xylocaine®, AstraZeneca, Germany), as described previously [29]. The whole os parietale and the caudal parts of the os frontale were removed using a liquid-cooled trephine, while the dura mater was left intact.

Afterward, the animals were randomized to treatment with EPO or placebo and MCAO was performed in each rat as discussed previously [15]. In brief, the right common carotid artery was exposed and a silicone-coated nylon suture (4-0) was inserted. Then the occluder was advanced proximally until its tip reached the anterior cerebral artery (mean suture depth: 20 ± 2 mm) beyond the carotid bifurcation, thus blocking the blood flow to the right MCA. Reperfusion was established after 90 minutes by removing the suture. Metamizole was administered orally again 6 h after the first application and added to the tap water.

Ethical approval: The research related to animal use has been complied with all the institutional guidelines and the current German animal protection law. The experiments were approved by the regional committee for the care and use of animals (Regierungspraesidium Darmstadt; Az.B2/170).

2.2 Experimental setup

One hundred and ten rats were randomly assigned to four groups: (i) placebo + craniectomy, (ii) EPO + craniectomy, (iii) placebo–craniectomy, and (iv) EPO–craniectomy.

Craniectomy was performed in 56 animals (+craniectomy); the bone skull of 54 rats was thinned but not completely removed (–craniectomy). Thereafter, all 110 rats were randomly subjected to the treatment groups (EPO vs. placebo): 15 minutes prior to MCAO, each animal was administered 5,000 IU/kg EPO (NeoRecormon®; Roche, Germany) in 2 ml isotonic saline (EPO) or only 2 ml isotonic saline (placebo) via coccygeal venous catheter. Afterward, MCAO was performed by a surgeon blinded to the group assignment. Functional testing took place at baseline and 24 h after MCAO. Then ten rats of each group were subjected to MRI to detect ischemic lesion volume, vascular edema, and midline shift (MLS) and to post-mortem quantification of BWC by the wet–dry technique. The remaining animals of each group underwent quantification of cerebral blood flow (CBF) via fpVCT. Functional assessment, radiological imaging, and evaluation, as well as wet–dry analysis, were performed by experienced investigators blinded to the group assignment.

2.3 Functional testing

Motor functions were assessed using the Rotarod test at baseline and 24 h after MCAO. The wheel was continuously accelerated from 0 to 30 rpm within 1 minute. The maximum speed tolerated by the rats was documented and the difference was calculated as Rotarod performance before and after MCAO [30].

2.4 MRI

After functional testing, the MRI scanning was performed under anesthesia with a tomography (Bruker PharmaScan 7.0 T, 16 cm), which operates at 300.51 MHz (1H-imaging) and is equipped with a 300 mT/m self-shielding gradient system. The animal's respiratory rate was monitored noninvasively and maintained between 60 and 80/min by regulation of the isoflurane concentration.

The linear polarized volume resonator (diameter 60 mm) was tuned and matched manually, and localized images were acquired using a spin-echo sequence. Rapid acquisition with relaxation enhancement sequences (20 contiguous slices of 1 mm thickness, repetition time [TR] = 2500 ms, and echo time [TE] = 41.8 ms) were used to verify symmetric positioning and were repeated after correction of the possible necessary slice angulation [18].

2.5 T2-imaging

To map the vascular edema (T2-relaxation time [T2RT]) [15] and the lesion and hemispheric volumes, we used a Carr–Purcell–Meiboom–Gill spin echo imaging sequence,

acquiring eight contiguous coronal slices (slice thickness = 2 mm, gap = 0 mm, field-of-view (FOV) = 37 × 37 mm, matrix size = 512 × 256, TR = 3833.5 ms, TE [12 echos, ΔTE = 18 ms] = 18–216 ms, number of excitations (NEX) = 1, and acquisition time (AT) = 12 min 7 s).

2.6 T2*-imaging

To exclude animals with possible hemorrhages, 16 contiguous coronal slices were acquired using an SNAP-T2*-imaging sequence (slice thickness = 1 mm, gap = 0 mm, FOV = 37 × 37 mm, matrix size 256 × 256, TR = 43.4 ms, TE = 7.0 ms, and AT = 12 min 7 s).

2.7 MRI data evaluation

2.7.1 Ischemic lesion volume

The mean ischemic lesion volume was determined by performing computer-aided planimetric assessment of the lesion volume (LV) and the hemispheric volumes of the T2-weighted images (ipsilateral: HV_i; contralateral: HV_c) (ImageJ v1.46; National Institutes of Health, Bethesda, USA). The edema-corrected lesion volume ($\%HLV_{ec}$) was calculated by the following equation [18]:

$$\%HLV_{ec} = ((HV_c - HV_i + LV)/HV_c) \times 100 \quad (1)$$

2.7.2 MLS quantification

The MLS quantification was performed using high-resolution T2-weighted images. The position of the third ventricle could be clearly determined in all rats. The distance between the middle of the third ventricle and the outer border of both hemispheres (distance from ipsilateral border to third ventricle: *A* and distance from contralateral border to third ventricle: *B*) was measured [17] and MLS was calculated by the following equation:

$$MLS = (A - B)/2 \quad (2)$$

2.7.3 T2RT

For quantification of the T2RT, we used Bruker's implemented image processing tool. On the six contiguous coronal slices, regions of interest (ROIs) were set in the center of the ischemic lesions in the cortex and subcortex and on the corresponding position of the contralateral hemisphere, and the side-to-side differences of the T2RT were calculated.

2.8 Postmortem analysis: quantification of BWC by the wet–dry technique

After MRI, the animals were deeply anesthetized and decapitated. The brains were removed and separated into the ipsi- and contralateral hemispheres. The wet weight of each hemisphere was measured, then the tissue was dried to a constant weight at 50°C and weighed again (dry weight). The absolute BWC ($\%H_2O$) was calculated as follows [18]:

$$\%H_2O = ([\text{wet weight} - \text{dry weight}]/\text{wet weight} \times 100) \quad (3)$$

Equation (4) was used to calculate the increase in BWC in the ipsilateral hemisphere compared to the unaffected contralateral hemisphere ($\%\Delta H_2O$) [18]:

$$\%\Delta H_2O = \%H_2O_{ipsilateral} - \%H_2O_{contralateral} \quad (4)$$

2.9 fpVCT

The CBF was quantified after the 24-h clinical testing with an fpVCT, which was developed by GE Healthcare, London, Ontario, Canada. The system is described in detail in the study by Obert et al. (2010) [31]. Preparation and anesthesia of the rats, image acquisition, reconstruction, and analysis followed a previously published protocol [32].

2.10 Placing the ROIs, infarct core, and hemisphere

Since the infarcted brain regions cannot be properly displayed on perfusion slices, the corresponding 2,3,5-triphenyltetrazolium chloride (TTC)-stained slices were used to identify the extent and location of ischemic areas. After VCT investigation, the animals were deeply anesthetized using isoflurane and euthanized by decapitation; the brains were removed and sectioned

coronally into six slices (thickness: 2 mm each), incubated in a 2% solution of TTC at 37°C, fixed by immersion in 10% buffered formalin solution, and scanned with a computer scanner (ScanJet 3400C; Hewlett Packard; resolution 600 × 600 dpi). The unstained areas of the fixed brain slices were defined as the ischemic infarction.

For ipsi- and contralateral sides, flexibly created freehand ROIs included cortical and subcortical regions of the infarct core as well as the whole hemisphere. The CBF (ml/100 g/min) was acquired as mean for each side or the corresponding region and in each animal, thus permitting comparison of data between infarct hemisphere and non-infarct hemisphere. Differences in CBF were calculated by the following equation:

$$\%\text{CBF difference} = (\text{mean CBF ipsilateral}/\text{mean CBF contralateral}) \times 100 \quad (5)$$

2.11 Statistical analysis

The Shapiro–Wilk test was used to test for normal distribution of parametric data. Homogeneity of variance was tested by the Levene test. Erythropoietin treatment and placebo groups were compared separately for craniectomy and sham craniectomy by unpaired Student's t test or, for data not passing the normality test, the nonparametric Mann–Whitney U test. Data are presented as mean ± standard deviation. The level of probability $p < 0.05$ was regarded as significant (SPSS v21; IBM, Germany).

3 Results

Twenty-six animals had to be excluded from this study: for seven animals, technical problems occurred during contrast agent infusion, and the imaging of another four rats was hampered due to motion artifacts. Seven animals suffered cerebral hemorrhage, six animals died during craniectomy, and two rats showed no ischemic infarction. The remaining 84 animals completed the study protocol.

Pre-MCAO Rotarod performance, body weight, and body temperature did not differ significantly between the groups.

3.1 Neurological impairment

The results in Rotarod test performance pre- vs. 24 h post-MCAO did not differ significantly between the craniectomy (5.71 ± 11.14 rpm vs. 6.29 ± 9.95 rpm; p = 0.837) and sham craniectomy groups (5.43 ± 11.21 rpm vs. 6.00 ± 7.10 rpm; p = 0.786).

3.2 Infarct size

Measurement by MRI of infarct sizes corrected for the space-occupying effect of brain edema revealed no difference ($t(18)$ = 1.391; p = 0.181, d = 0.62) between craniectomy rats receiving placebo (36.29 ± 10.21%) vs. EPO (30.34 ± 8.86%). The mean ischemic lesion volume after 24 h was significantly smaller ($t(18)$ = 2.497; p = 0.022, d = 1.12) in EPO-treated animals without craniectomy (25.28 ± 7.03%) when compared to placebo animals without craniectomy (34.83 ± 9.84%) (Figure 1).

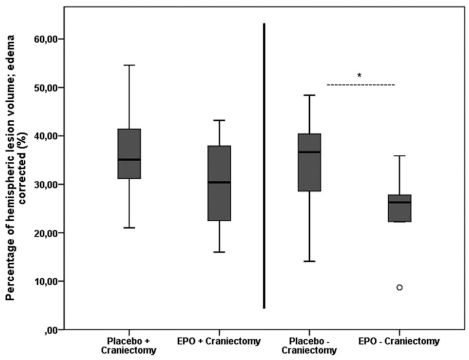

Figure 1: Mean ischemic lesion volume as determined on MRI, expressed in percentage of hemispheric volume (%HLV_{ec}). Significantly reduced mean ischemic lesion volume for EPO-treated animals compared to the placebo group without craniectomy (*p = 0.022; t-test). No significant difference could be detected between craniectomy groups. Outliers are marked with a circle (out values) or a star (far out values).

3.3 Brain edema

The MLS of the animals treated with EPO (0.083 ± 0.027 cm), which were not craniectomized, was significantly reduced ($t(18)$ = 2.768; p = 0.013; d = 1.24) when

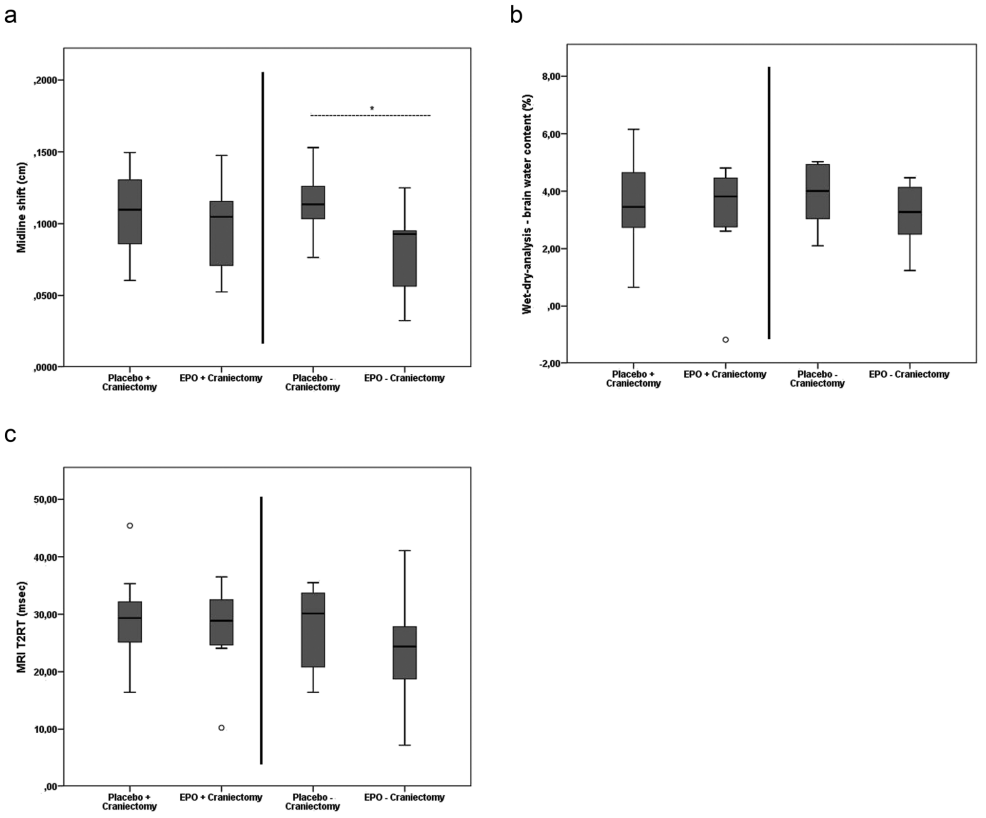

Figure 2: MLS (a), BWC (b), and T2RT (c). (a) MLS in the groups without craniectomy was significantly smaller in animals treated with EPO when compared to the placebo animals (*p = 0.013). No significant differences were observed within the craniectomy groups. (b) BWC and (c) T2RT displayed no significant differences between the groups. Outliers are marked with a circle (out values) or a star (far out values).

compared to the noncraniectomized placebo animals (0.114 ± 0.023 cm). This could not be observed in the two craniectomy groups (placebo: 0.109 ± 0.029 cm vs. EPO: 0.100 ± 0.031 cm, respectively; $t(18) = 0.613$; $p = 0.548$; $d = 0.30$) (Figure 2a).

In the EPO- and placebo-treated craniectomy groups, BWC (placebo: 3.33 ± 1.75% vs. EPO: 3.48 ± 1.61%, respectively; $z = 1.71$; $p = 0.912$; $d = 0.09$) and T2RT (placebo: 29.50 ± 7.79 ms vs. EPO: 27.57 ± 7.39 ms, respectively; $t(18) = 0.569$; $p = 0.576$; $d = 0.25$) showed no significant difference. A similar result could be obtained from the analyses of BWC (placebo: 3.87 ± 1.02% vs. EPO: 3.19 ± 1.11%; $z = -1.21$; $p = 0.247$; $d = 0.64$) and T2RT (placebo: 28.25 ± 6.65 ms vs. EPO: 23.54 ± 9.14 ms; $t(18) = 1.318$; $p = 0.204$; $d = 0.59$) in noncraniectomy groups III + IV (Figure 2b and c).

3.4 CBF

CBF was acquired within cortical and subcortical regions of the infarct core as well as the whole hemisphere and expressed as a ratio between the ipsilateral and the contralateral sides.

In the absence of craniectomy (groups III + IV), the EPO-treated animals showed a significant increase in CBF in cortical regions of the infract core when compared to

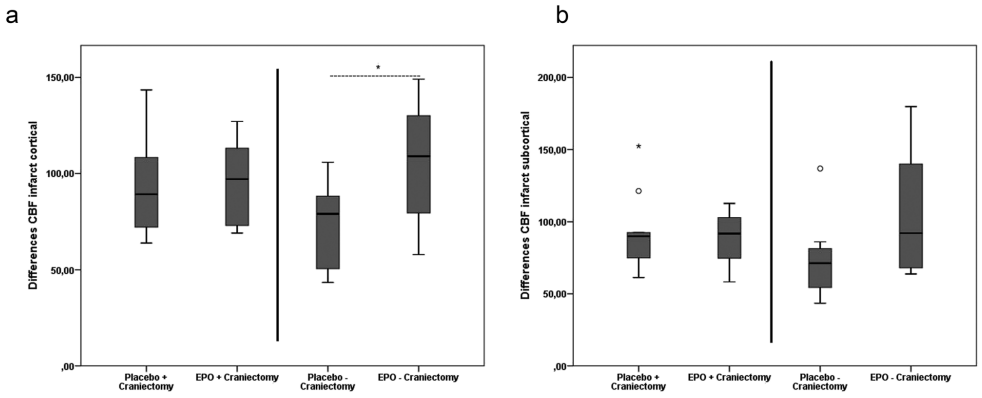

Figure 3: CBF in the infarct core. There was a significant CBF increase with EPO treatment in the cortical regions of the infarct core when compared to placebo treatment in the absence of craniectomy (*p = 0.043 u-test) (a). No significant CBF changes could be observed in the cortical regions of the infarct core when craniectomy was performed (a) or in subcortical regions (b). Outliers are marked with a circle (out values) or a star (far out values).

the placebo-treated animals (placebo: 72.29 ± 24.00% vs. EPO: 105.53 ± 33.10%, respectively; $t(18) = -2.245$; $p = 0.043$; $d = 1.00$) (Figure 3a). In the subcortical regions (placebo: 74.29 ± 29.04 vs. EPO: 103.38 ± 39.54%, respectively; $t(18) = -1.799$; $p = 0.091$; $d = 0.85$) and the total infarct core (placebo: 76.58 ± 28.03 vs. EPO: 104.48 ± 33.49%, respectively; $t(18) = -1.975$; $p = 0.065$; $d = 0.90$), tendencies did not reach statistical significance. No significant difference in CBF was observed in the cortical (placebo: 94.40 ± 28.62% vs. EPO: 95.12 ± 23.79%, respectively; $t(18) = -0.05$; $p = 0.961$; $d = 0.03$) or subcortical region (placebo: 88.94 ± 19.00% vs. EPO: 92.74 ± 26.73%, respectively; $t(18) = 0.378$; $p = 0.709$; $d = 0.16$) or the whole infarct core within the craniectomy groups (placebo: 90.89 ± 20.39% vs. EPO: 96.67 ± 28.19%, respectively; $t(18) = 0.542$; $p = 0.594$; $d = 0.23$) (groups I + II, Figure 3).

Between the craniectomy groups, investigation of hemispherical blood flow in the cortical (placebo: 108.59 ± 19.46% vs. EPO: 103.75 ± 11.68%, respectively; $t(18) = 0.706$; $p = 0.488$; $d = 0.30$) and subcortical regions (placebo: 96.94 ± 7.15% vs. EPO: 94.11 ± 11.30%, respectively; $t(18) = 0.699$; $p = 0.492$; $d = 0.29$) and total hemisphere (placebo: 103.70 ± 15.81% vs. EPO: 100.13 ± 10.96%, respectively; $t(18) = 0.616$; $p = 0.545$; $d = 0.26$) revealed no significant effects of EPO treatment. Similar results were shown in the comparison of CBF between groups III + IV without craniectomy in the cortical (placebo: 91.25 ± 16.45% vs. EPO: 99.12 ± 18.04%, respectively; $t(18) = -1.020$; $p = 0.312$; $d = 0.46$) and subcortical regions (placebo: 90.02 ± 11.54% vs. EPO: 90.43 ± 9.18%, respectively; $t(18) = -0.087$; $p = 0.931$; $d = 0.04$) and total hemisphere (placebo: 91.26 ± 11.86% vs. EPO: 94.36 ± 10.90%, respectively; $t(18) = -0.609$; $p = 0.550$; $d = 0.27$) (Figure 4).

5 Discussion

Investigations on rodent stroke models [16–18,33] indicate that the development of vasogenic brain edema within the hyperacute phase of stroke (<6 h) may exert a significant, possibly underestimated, influence on the progression of ischemic area, as swelling of ischemic tissue within the fixed cranial volume can lead to impairment of microcirculation in the critically hypoperfused penumbral area. Hence, collateral damage caused by the space-occupying effect of a large MCA territory stroke accounts for up to 50% of ischemic lesion formation [16]. Therapeutic measures aiming to reduce cerebral edema and its resulting space-occupying effect in the early stages of stroke may operate as indirect or "secondary" neuroprotectants [16,29]. Investigations on the effects of systemically administered rhEPO prior to transient MCAO in rodents suggest that neuroprotection results more from the mitigation of brain edema than from direct antiapoptotic effects on neurons [27]. We hypothesized that EPO administered prior to transient MCAO exerts its neuroprotective properties in the early phase of stroke primarily via secondary neuroprotection by reduction of cerebral edema.

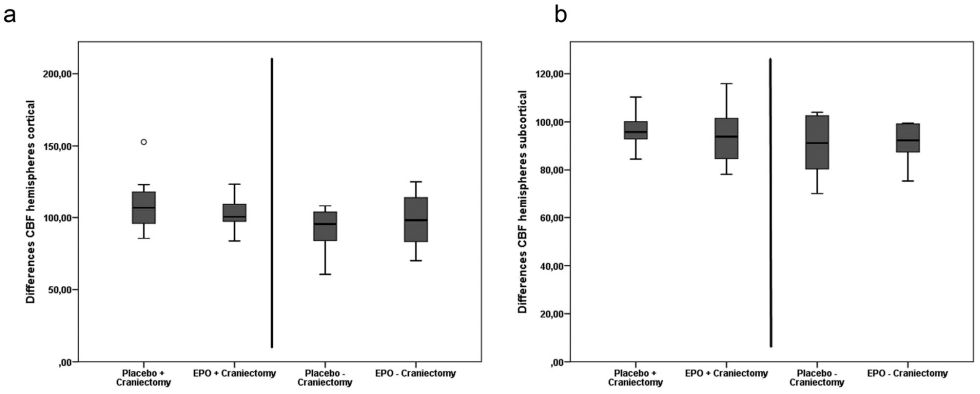

Figure 4: CBF in the hemisphere. The CBF measurement of the whole hemispheres, i.e., cortical (a) and subcortical (b) regions, revealed no significant effects of EPO treatment regardless of craniectomy. Outliers are marked with a circle (out values).

Craniectomy has been shown to save the lives of patients with large space-occupying territorial strokes in severe danger of cerebral herniation and death and was proven in large clinical trials to reduce mortality significantly, from 71 to 22% [34,35]. Experimental studies on the effect of craniectomy in a rodent model of MCAO report a significant reduction of infarct size, mainly attributed to the release of mechanical compression [36,37]. To approach the distinction of primary from secondary neuroprotection in our study, elimination of increased intracranial pressure due to the space-occupying ischemia was achieved by bilateral craniectomy prior to transient MCAO [16,29]. Thus, the preponderance of edema reduction via EPO was expected to lead to pronounced group differences regarding infarct size and edema volume, which are dependent on integrity of the skull.

We observed that rhEPO treatment before transient MCAO reduced edema-corrected infarction size by approximately 10%. Data on experiments with a comparable setting are limited; two previous studies on rats reported no significant effects on infarct volume for EPO pretreatment. In contrast, a study on mice showed infarct reduction up to 47% [27,38,39]. Interestingly, in the present investigation, a significant reduction compared to placebo treatment could only be observed if the skull was left intact; an approximation of infarct sizes could be quantified with craniectomy.

Experimental research on rodent stroke models provides robust evidence for the antiedematic effects of EPO, which has particularly been attributed to a preserved barrier function of the BBB [40–45]. An investigation on the markers of BBB integrity – such as occludin, alpha-, and beta-catenin – demonstrated that EPO treatment before and 3 days after focal cerebral ischemia can stabilize the BBB, reduce its permeability, and thereby control cerebral inflammation and edema [43]. Impermeability of the BBB mainly depends on intact endothelial cells and tight junctions, which are subjected to substantial oxidative stress by generation of reactive oxygen species and lipid peroxidation during the phase of reperfusion after transient ischemia [46,47]. Under this condition, EPO seems to stimulate endothelial nitric oxide production and has the ability to prevent reperfusion-mediated injury to the BBB [48]. Due to the fact that lesion volume is proportional to hemispheric BWC, the volume of infarcted tissue can bias methods for quantification of BWC that include whole hemispheres, such as the wet–dry technique and determination of MLS; cerebral edema in the present investigation was therefore assessed on MRI using T2RT measurements in ROIs, since this method was shown to be largely independent of lesion size [18]. We could demonstrate a significant reduction in MLS for EPO pretreatment only in the absence of bilateral craniectomy. In this group, MRI T2RT presented a trend toward the lowest mean values for the treatment group with intact skull but missed statistical significance. Nevertheless, these data seem to suggest that neuroprotection of EPO pretreatment in transient MCAO implies a strong antiedematic effect.

We used fpVCT for noninvasive dynamic imaging of cerebral perfusion after temporary MCAO in the cortical and subcortical regions of the infarct and the whole hemisphere [32]. Without craniectomy, the EPO

pretreatment led to a significant increase in CBF in the cortical regions of the ischemic tissue. However, in subcortical areas of the infarct and the whole hemispheres, no significant alterations of CBF could be objectified. Xiong et al. described EPO neuroprotection after traumatic brain injury even in EpoR null mice and attributed this effect particularly to vascular protection [49]. Li et al. investigated angiogenesis in mice that received rhEPO 30 minutes before and once daily after ischemic stroke and observed enhanced angiogenic activity between days 7 and 21; on day 14, the CBF reached preischemia initial values [50]. Furthermore, in a rabbit model for subarachnoid hemorrhage, intravenously administered rhEPO led to a significantly increased CBF between days 2 and 16 [51]. In addition to these observations of EPO's time-sensitive effects, Shafi et al. used isolated rat MCA to demonstrate that luminal-applied EPO can directly dilate arteries and that 24-h pretreatment with EPO potentiates this effect [52]; after this single-dose pretreatment with EPO and transient MCAO, we only observed a significant increase in CBF in the defined cortical regions of the infarct and in the absence of craniectomy. If compression on the brain, microvasculature and presumable pial and venous vessels is released by craniectomy, the CBF in EPO- and placebo-treated rats is equal. This seems to display a local effect for the defined area of the ischemia, as no differences in CBF could be observed for total hemispheres regardless of the EPO treatment or craniectomy. A focal improvement in CBF in the cortical regions of the ischemic area may indicate a more efficient collateralization with EPO, either via its antiedemic and pressure-reducing mode of action or due to its direct vasodilatative effects. Improved collateralization in turn supports the recovery of critically perfused penumbral areas reducing the infarct core, which has been shown by a significant reduction in ischemic lesion volume. In line with the aforementioned data on infarct size and edema reduction, the latter could only be objectified in the absence of craniectomy, i.e., a situation in which pressure variations are supposed to be the most pronounced.

The results of this study have to be interpreted with caution, as surrogate parameters for a secondary neuroprotective mechanism of action were considered. These can be regarded as hypothesis generating but must subsequently be confirmed in the corresponding mechanistic studies to objectively distinguish a direct or indirect mechanism of action.

In this study, rhEPO was administered – a compound that, because of its low BBB permeability, must be applied in comparatively high intravenous doses, prompting several dose-dependent side effects such as increased hematocrit and hypertension as well as procoagulatory and prothrombotic effects on microcirculation. These side effects seem to be primarily due to the erythropoietic mode of action of the EPO derivate, and it is conceivable in principle that they limit the extent of neuroprotection in the context of acute cerebrovascular diseases. Therefore, efforts have been made in the past to support EPO-mediated cytoprotection without affecting the hematopoietic system. In this respect, it could be shown that, putatively due to an altered receptor interaction, carbamylated EPO and mutants such as EPO-S100E or EPO-R103E act neuroprotectively but lack erythropoietic activity with a drastically reduced $(EPOR)_2$ affinity. In addition, the fusion protein EPO-Tat possesses a significantly enhanced BBB permeability and thus enables the use of lower effective doses [53,54]. It therefore remains to be discussed whether the use of another EPO derivative yielded different, clearer results.

Another aspect of pharmacokinetics appears to be of particular interest in connection with the application of EPO prior to MCAO. In a rodent model of traumatic brain injury, it was shown not only that EPO must be administered in high doses when applied peripherally and that intravenous is superior to intraperitoneal administration but also that rhEPO crosses the BBB with a delay of approximately 4 h and appears to develop its biological effect after around 8 h [1]. Moreover, the half-life of rhEPO after single injection was reported to be between 25.6 h and 35.5 h [2]. If this time frame of pharmacokinetics and the edema dynamics after cerebral infarction with the onset immediately after ischemia are taken into account, an even earlier time of application of EPO could possibly have led to a more pronounced neuroprotective effect. Thus, the single administration of EPO immediately after the onset of ischemia, which is more similar to the clinical situation in stroke, is not expected to produce significantly different results. As described in the introduction, the timing was chosen against the background of anticipatory neuroprotection in cerebrovascular interventions, for example, where the onset of damage is known; a transfer of the results to acute stroke therapy is only possible with difficulty.

With respect to the effect sizes of infarct volumes and perfusion parameters, although the number of animals per group seems to be sufficient, it remains debatable whether larger groups for investigations on brain edema would have led to significantly different results.

Clinical testing did not point out a statistically significant functional improvement, which might indicate limited sensitivity of the clinical tests in general or with regard to the chronological parameters and points in time selected in this study. Furthermore, the study design does not allow quantification of possible long-term improvement. In principle, the use of healthy animals, controlled laboratory conditions, and application of anesthesia can hamper the assignability of findings from bench to bedside, which has to be considered when findings are interpreted.

6 Conclusion

Interventions for predictable stroke risk substantiate discussion on anticipatory neuroprotection preceding the risk-related procedure and intended for prevention of neuronal loss. This study demonstrates that a single dose of rhEPO 5,000 IU/kg given prior to transient MCAO in rats significantly reduces ischemic lesion volume, decreases MLS, and increases local CBF in the cortical regions of ischemia after 24 h. Data may suggest an interaction between edema and pressure reducing as well as blood flow-increasing effects mediated by EPO.

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Conflict of interest: The authors states no conflict of interest.

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5. Abkürzungsverzeichnis

ACM	Arteria cerebri media
ADC	apparent diffusion coefficient
BBB	blood-brain-barrier
BWC	brain-water content
CABG	coronary artery bypass grafting
CAM	cerebral air microembolisation
CBF	cerebral blood flow
cEEG	kontinuierliche Elektroenzephalographie (continuous electroencephalography)
CFQ	cognitive failure questionnaire
$CMRO_2$	cerebral metabolic rate of oxygen utilization
DAMP	damage-associated molecular patterns
DSM-5	Diagnostic and Statistical Manual of mental Disorders - 5
DWI	diffusion weighted imaging
ECC	extracorporeal circulation
EEG	Elektroenzephalographie
EPO	Erythropoietin
ERC	European Resuscitation Council
ESICM	European Society of Intensive Care Medicine
f-CFQ	cognitive failure questionnaire - Fremdeinschätzung
fpVCT	flat-panel volume computed tomography
HADS	Hospital Anxiety and Depression Scale
HLM	Herz-Lungen-Maschine
HV	Hemisphärenvolumen
ICDSC	Intensive Care Delirium Screening Checklist
LV	Läsionsvolumen
MAP	mittlerer arterieller Blutdruck (mean arterial pressure)
MCAO	middle cerebral artery occlusion
MCI	mild cognitive impairment
MRT	Magnetresonanztomographie
NCS	non-convulsive seizures
PH	pedunkuläre Halluzinose
POCD	postoperative cognitive deficits
POCI	postoperative cognitive improvement
rhEPO	rekombinantes humanes Erythropoietin
ROI	region of interest
s-CFQ	cognitive failure questionnaire - Selbsteinschätzung

SIRS	systemisches inflammatorisches Response-Syndrom
TNF	Tumornekrosefaktor

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8. Erklärung

Hiermit erkläre ich, dass ich die mir zuzuordnenden Teile im Rahmen der kumulativen Habilitationsschrift selbstständig und ohne unzulässige Hilfe oder Benutzung anderer als der angegebenen Hilfsmittel angefertigt habe. Alle Textstellen, die wörtlich oder sinngemäß aus veröffentlichten oder nichtveröffentlichten Schriften entnommen sind, und alle Angaben, die auf mündlichen Auskünften beruhen, sind als solche kenntlich gemacht. Ich versichere, dass ich für die nach §2 (3) der Habilitationsordnung angeführten bereits veröffentlichten Originalarbeiten als Erst- oder Seniorautor fungiere, da ich den größten Teil der Daten selbst erhoben habe, für das Design der Arbeit verantwortlich bin und die Manuskripte maßgeblich gestaltet habe. Für alle von mir erwähnten Untersuchungen habe ich die in der „Satzung der Justus-Liebig-Universität zur Sicherung guter wissenschaftlicher Praxis“ niedergelegten Grundsätze befolgt. Ich versichere, dass alle an der Finanzierung der Arbeit beteiligten Geldgeber in den jeweiligen Publikationen genannt worden sind. Ich versichere außerdem, dass die vorliegende Arbeit weder im Inland noch im Ausland in gleicher oder ähnlicher Weise einer anderen Prüfungsbehörde vorgelegt wurde oder Gegenstand eines anderen Prüfungsverfahrens war. Mit der Überprüfung meiner Arbeit durch eine Plagiatserkennungssoftware bzw. ein internetbasiertes Softwareprogramm erkläre ich mich einverstanden.

Gießen, im Januar 2022

Martin Jünemann