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H A B I L I T A T I O N S S C H R I F T

„Schlaganfallassoziierte Komorbiditäten unter besonderer Berücksichtigung metabolischer Aspekte“

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Abkürzungsverzeichnis

ACh	Acetylcholin
ANS	Autonomes Nervensystem
ASMI	Appendikulärer Skelettmuskel-Index
ATP	Adenosintriphosphat
BI	Barthel Index
BL	Baseline
BIA	Bioelektrische Impedanz Analyse
BMI	Body Mass Index
CAF	C-terminales Agrin Fragment
CHI	Chronische Herzinsuffizienz
CFD	Cumulative Funktional Disability (kumulative funktionelle Beeinträchtigung)
CKD	Chronische Niereninsuffizienz
COPD	Chronische obstruktive Lungenerkrankung
CrP	C-reaktives Protein
CT	Computertomographie
Da	Dalton
DEXA	Duale X-Ray Absorptiometrie
ED	Endotheliale Dysfunktion
EKG	Elektrokardiogramm
ESUS	Embolic stroke of unknown source (embolischer Schlaganfall unbekannter Ursache)
FU	Follow-up
HGS	Handgriff Stärke
HRV	Herzratenvariabilität
ID	Iron Deficiency (Eisenmangel)
IL-6	Interleukin 6
KHK	Koronare Herzkrankheit
LVEF	Linksventrikuläre Auswurffraktion

MCA	Arteria cerebri media
MCAO	Middle cerebral artery occlusion
MHC	Myosin Heavy Chain
mRS	Modified Rankin Scale
MRT	Magnetresonanztomographie
MUNE	Motor unit number estimate
NIHSS	National Institute of Health Stroke Scale
OSA	Obstruktive Schlafapnoe
RHI	Reaktiver Hyperämie-Index
RMA	Rivermead Motor Assessment
SDB	Sleep-disordered Breathing (Schlafbezogene Atemstörungen)
SMMI	Skelettmuskelmasseindex
TIA	Transitorische ischämische Attacke
TNF-α	Tumornekrosefaktor alfa
TOAST	Trial of ORG 10172 in Acute Stroke Treatment
TSAT	Transferrin-Sättigung
VHF	Vorhofflimmern
WHO	Weltgesundheitsorganisation

1. Einleitung

Metabolische Komorbiditäten sind für den klinischen Verlauf vieler Erkrankungen inklusive Schlaganfall relevant. Das anabole/katabole Ungleichgewicht und Auftreten systemischer Inflammation im Rahmen eines Schlaganfalls können das Stoffwechselgleichgewicht beeinträchtigen und eine Reihe von metabolischen Komorbiditäten hervorrufen. Das klinische Bild und Prognose eines Schlaganfalls werden somit nicht nur von der Schwere der neurologischen Defizite, sondern auch von den begleitenden metabolischen Komplikationen geprägt. Das zunehmende Interesse liegt aktuell in der interdisziplinären Erforschung metabolischer Folgen nach Schlaganfall [1]. Ein Verlust von Körpergewicht [2] oder Muskelmasse [3,4], das Auftreten von schlafbezogenen Atemstörungen [5], Anämie [6] oder von endothelialer Dysfunktion [7] ist in vielen Fällen schleichend, sodass diese Komorbiditäten oft erst gar nicht erkannt werden. Allerdings sind sie für den klinischen Verlauf prognostisch relevant und können den Rehabilitationsverlauf, die Lebensqualität, die physische Ausdauer und psychisches Befinden des Patienten deutlich beeinträchtigen. Ein frühes Erkennen und effektive Behandlung metabolischer Komorbiditäten würde die klinische Prognose von Patienten nach Schlaganfall verbessern.

1.1 Schlaganfall – allgemeine Aspekte

Mit einer Prävalenz über 101 Millionen Fälle im Jahr 2019 gehört der Schlaganfall zu der dritthäufigsten Todes- und Behinderungsursache im Erwachsenenalter weltweit [8,9,10]. Die globalen Kosten für Behandlung, Prävention und Rehabilitation vom Schlaganfall betragen über 721 Mrd. US-Dollar [8]. Die Behandlung von Patienten mit akutem Schlaganfall erfolgt in der Regel auf spezialisierten Einheiten, Stroke-Units, und erfordert eine effektive Zusammenarbeit eines gut geschulten multiprofessionellen Teams bestehend aus Ärzten, Pflege, Physiotherapeuten und Sozialarbeitern [11,12]. Im Akutstadium erfolgt neben der Einleitung bzw. Durchführung einer Akuttherapie und einem kontinuierlichen Monitoring der kardiovaskulären Parameter auch eine interdisziplinäre Diagnostik und Ausschalten von Ursachen des Schlaganfalls [12]. Weitere Funktionen des Stroke-Unit schließen die Einleitung einer frühzeitigen Physiotherapie, Prävention und Behandlung von Komplikationen, Organisation der Anschlussbehandlung (Rehabilitation) und

Betreuung von Angehörigen ein [12]. Eine Behandlung in der Stroke-Unit verbessert das klinische Outcome nach Schlaganfall [11].

1.1.1 Ätiologie des Schlaganfalls

Schlaganfälle werden in ischämische (ca. 85%) und hämorrhagische (15%) Hirninfarkte eingeteilt. Ätiologisch erfolgt die Einteilung von ischämischen Schlaganfällen anhand der „Trial of ORG 10172 in Acute Stroke Treatment (TOAST) Kriterien“ in fünf Infarkttypen: makroangiopathische, mikroangiopathische und kardioembolische Infarkte, Hirninfarkte durch unklare Ursachen (bei zwei konkurrierenden Infarkttypen) und durch andere Ursachen (z.B. Grunderkrankung) [13]. Die ätiologische Genese vom kryptogenen Schlaganfall war in den letzten Jahren ein Gegenstand von intensiven Untersuchungen [14,15]. Die klinischen Studien deuten darauf hin, dass als Ursachen z. B. unbekanntes Vorhofflimmern (VHF) [16], persistierendes Foramen ovale [17], Kardiomyopathien oder große arterielle Plaques [18] dem kryptogenen Schlaganfall zugrunde liegen können. Der kryptogene Schlaganfall wird somit als ein thromboembolischer Schlaganfall unbestimmter Quelle (ESUS, embolic stroke of unknown source) definiert und anhand der TOAST Klassifikation dem Subtyp „unklare Ursache“ zugeordnet.

1.1.2 Neurologische Skalen

Der Schweregrad von neurologischen Defiziten, funktionellem Status und der Lebensqualität nach Schlaganfall wird in der Klinik anhand der validierten Skalen bestimmt. In diesem Abschnitt werden für diese Arbeit relevante Skalen erläutert.

Die Partizipation, Hilfebedürftigkeit und Lebensqualität nach Schlaganfall werden anhand des modified Rankin Scale (mRS) beurteilt. Die mRS beurteilt das klinische Outcome nach Schlaganfall anhand von 6 Kategorien, die von „0“ bis „6“ reichen, wobei Kategorie 0 „Keine Symptome“ und Kategorie 6 „Tod“ bedeutet (Tabelle 1) [19].

Die neurologischen Defizite werden anhand der NIHSS (National Institute of Health Stroke Scale) erfasst (Tabelle 2). Diese Skala schließt 13 Kategorien mit einer maximalen Punktzahl von 42 ein,

wobei die Werte von 0 bis 12 Punkten auf einen leicht- bis mittelgradigen neurologischen Defizit hindeuten [19].

Die Funktions- und Aktivitätsstörungen werden mittels Barthel-Index (BI) und Rivermead Motor Assessment (RMA) erfasst.

Der BI umfasst 10 Kategorien mit grundlegenden Aktivitäten des täglichen Lebens in Bezug auf Selbstversorgung und Mobilität mit Werten von „0“ bis „100“ (s. Anhang, Tabelle A1). Die niedrigeren Werte deuten auf eine größere Abhängigkeit des Patienten hin [19].

Das RMA wird in der neurologischen Rehabilitation angewendet. Die Skala wertet die sensomotorischen Störungen aus und enthält 13 Fragen, die mit „ja“ oder „nein“ beantwortet werden [20]. Eine höhere Punktzahl deutet den geringeren Grad der Behinderung an (s. Anhang, Tabelle 1B).

Tabelle 1. Modified Rankin Scale [19].

mRS	**Charakteristik**
0	Keine Symptome.
1	Keine relevante Beeinträchtigung. Kann trotz gewisser Symptome Alltagsaktivitäten verrichten.
2	Leichte Beeinträchtigung. Kann sich ohne Hilfe versorgen, ist aber im Alltag eingeschränkt.
3	Mittelschwere Beeinträchtigung. Benötigt Hilfe im Alltag, kann aber ohne Hilfe gehen.
4	Höhergradige Beeinträchtigung. Benötigt Hilfe bei der Körperpflege, kann nicht ohne Hilfe gehen.
5	Schwere Behinderung. Bettlägerig, inkontinent, benötigt ständige pflegerische Hilfe.
6	Tod.

Tabelle 2. National Institute of Health Stroke Scale [19,21].

1a	Bewusstseinslage (Vigilanz)	(0) **Wach**, unmittelbar antwortend. (1) **Benommen**, aber durch geringe Stimulation zum Befolgen von Aufforderungen, Antworten oder Reaktionen zu bewegen. (2) **Somnolent**, bedarf wiederholter Stimulation um aufmerksam zu sein, oder ist soporös und bedarf starker oder schmerzhafter Stimulation zum Erzielen von Bewegungen. (3) **Koma**, antwortet nur mit motorischen oder vegetativen Reflexen oder reagiert gar nicht, ist schlaff und ohne Reflexe. *Anmerkung: bei Koma erhält Skala 7 (Extremitätenataxie) 0 Punkte.*
1b	Orientierung	**Frage nach Monat und Alter** (0) beide Fragen richtig beantwortet. (1) eine Frage richtig beantwortet. (2) keine Frage richtig beantwortet.
1c	Befolgung von Aufforderungen	**Aufforderung die Augen und die nicht paretische Hand zu öffnen und zu schließen** (0) beide Aufforderung richtig befolgt. (1) eine Aufforderung richtig befolgt. (2) keine Aufforderung richtig befolgt.
2	Blickbewegungen (Oculomotorik)	(0) Normal. (1) Partielle Blickparese = wenn die Blickrichtung von einem oder beiden Augen abnormal ist, jedoch keine forcierte Blickdeviation oder komplette Blickparese besteht (e. g. Augenmuskelparese). *Auch bei unzureichender Kooperation 1 Pkt.* (2) Forcierte Blickdeviation oder komplette Blickparese, die durch Ausführen des oculocephalen Reflexes nicht überwunden werden kann.
3	Gesichtsfeld	(0) keine Einschränkung. (1) partielle Hemianopsie. (2) komplette Hemianopsie. (3) bilaterale Hemianopsie (Blindheit oder corticale Blindheit). *Anmerkung: Bei fehlender Beurteilbarkeit 0 Punkte.*
4	Facialisparese	(0) normal. (1) gering (abgeflachte Nasolabialfalte, Asymmetrie beim Lächeln). (2) partiell (vollständige oder fast vollständige Parese des unteren Gesichts). (3) vollständig auf einer oder beiden Seiten (fehlende Bewegungen unterer und oberer Teil des Gesichts).
5	Motorik Arme getrennt für links und rechts z. B. bei Tetraparese	(0) kein Absinken (der Arm wird über 10 Sekunden in der 90º/45º Position gehalten) (1) Absinken (der Arm wird zunächst bei 90º/45º gehalten, sinkt aber im Verlauf von 10 Sek. ab. (2) Anheben gegen Schwerkraft möglich (der Arm kann die 90º/45º Position nicht erreichen oder halten, sinkt auf die Liegefläche ab, kann aber gegen Schwerkraft angehoben werden) (3) Kein (aktives) Anheben gegen Schwerkraft, der Arm fällt nach passivem Anheben sofort auf die Liegefläche. (4) Keine Bewegung. *Anmerkung: bei Amputation oder Gelenkversteif. 0 Punkte; bei Plegie erhält Skala 7 (Extremitätenataxie) 0 Punkte.*

6	Motorik Beine getrennt für links und rechts z. B. bei Tetraparese	(0) Kein Absinken (das Bein bleibt über 5 Sekunden in der 30º Position). (1) Absinken (das Bein sinkt am Ende der 5 Sekundenperiode, berührt aber die Liegefläche nicht). (2) Aktive Bewegung gegen die Schwerkraft (das Bein sinkt binnen 5 Sek. auf die Liegefläche ab, kann aber gegen die Schwerkraft gehoben werden). (3) Kein (aktives) Anheben gegen die Schwerkraft, das Bein fällt nach passivem Anheben sofort auf die Liegefläche. (4) Keine Bewegung. *Anmerkung: bei Amputation oder Gelenkversteif. 0 Punkte; bei Plegie erhält Skala 7 (Extremitätenataxie) 0 Punkte.*
7	Extremitätenataxie	(0) fehlend. (1) in einer Extremität vorhanden. (2) in zwei Extremitäten vorhanden. Anmerkung: *wird bei Verständigungsschwierigkeiten oder Plegie als fehlend (0 Punkte.) gewertet.* *wird bei Angabe von Koma (s. Skala 1a) als fehlend (0 Punkte.) gewertet.*
8	Sensibilität	(0) Normal; kein Sensibilitätsverlust. (1) Leichter bis mittelschwerer Sensibilitätsverlust; Patient empfindet Nadelstiche auf der betroffenen Seite als stumpf, oder er nimmt diese nur als Berührung wahr. (2) Schwerer bis vollständiger Sensibilitätsverlust; Patient nimmt die Berührung von Gesicht, Arm und Bein nicht wahr.
9	Sprache	(0) normal; keine Aphasie. (1) Leichte bis mittelschwere Aphasie; deutliche Einschränkung der Wortflüssigkeit oder des Sprachverständnisses, keine relevante Einschränkung von Umfang oder Art des Ausdruckes. Die Einschränkung des Sprachvermögens und/oder des Sprachverständnisses macht die Unterhaltung schwierig bis unmöglich. (2) Schwere Aphasie; die Kommunikation findet über fragmentierte Ausdrucksformen statt. Der Untersucher muss das Gesagte in großem Umfang interpretieren, nachfragen oder erraten. Der Untersucher trägt im wesentlichen die Kommunikation. (3) Stumm, globale Aphasie; Sprachproduktion oder Sprachverständnis nicht verwertbar (auch bei Koma).
10	Dysarthrie	(0) Normal. (1) Leicht bis mittelschwer; der Patient spricht zumindest einige Worte verwaschen und kann nur mit Schwierigkeiten verstanden werden. (2) Schwer, anarthrisch; die verwaschene Sprache des Patienten ist unverständlich und beruht nicht auf einer Aphasie. *Anmerkung: Bei Intubation o. ä. 0 Punkte*
11	Neglect	(0) Keine Abnormalität. (1) Visuelle, taktile, auditive oder personenbezogene Unaufmerksamkeit oder Auslöschung bei Überprüfung von gleichzeitiger bilateraler Stimulation in einer der sensiblen Qualitäten. (2) Schwere halbseitige Unaufmerksamkeit. Kein Erkennen der eigenen Hand oder Orientierung nur zu einer Seite des Raumes. *Anmerkung: bei fehlender Beurteilbarkeit 0 Punkte*

1.2 „Obesity Paradox“ und Schlaganfall

Laut Klassifikation der Weltgesundheitsorganisation (WHO) für Erwachsene Personen älter als 20 Jahre steht ein Body Mass Index (BMI) von 18,5 bis 24,9 kg/m² für Normalgewicht, von 25 bis 30 kg/m² für Übergewicht und BMI>30 kg/m² für Adipositas [22]. Der BMI wird als Verhältnis vom Körpergewicht in Kilogramm zur Größe in Meter in Quadrat errechnet. Diese Formel wurde vom belgischen Mathematiker Quételet entwickelt [23]. Die WHO empfiehlt das Körpergewicht innerhalb der empfohlenen Grenzen für Normalgewicht zu halten denn Übergewicht, Adipositas und Gewichtszunahmen gehören zu den kardiovaskulären und zerebrovaskulären Risikofaktoren [24,25,26].

Allerdings häufen sich die Beweise dass das Überleben und die klinische Prognose von Patienten mit chronischen Erkrankungen inklusive Schlaganfall durch Übergewicht und Adipositas positiv beeinflusst werden [27]. Es wurden U- bzw. J-förmige Verteilungen von klinischen Outcome in Abhängigkeit vom BMI nach Schlaganfall beobachtet. Die Studien berichten von geringeren Invaliditätsraten und verbesserter Lebensqualität nach Schlaganfall [28], sowie von besserem Überleben [29] bei übergewichtigen und adipösen Patienten im Vergleich zu Patienten mit normalem BMI. Die TEMPiS (Telemedical Project for Integrative Stroke Care) Studie, die über 4000 Patienten mit transitorischer ischämischer Attacke (TIA) oder akutem Schlaganfall in einem Zeitraum von 30 Monate nachverfolgte, zeigte eine geringere Gesamtmortalität, weniger wiederkehrende Schlaganfälle, sowie eine geringere funktionelle Beeinträchtigung bei adipösen und übergewichtigen Patienten [30]. Darüber hinaus wurde bei adipösen und übergewichtigen Patienten im Vergleich zu Patienten mit normalem BMI, die am Athens Stroke Outcome-Projekt teilnahmen, ein signifikant geringeres Risiko für die 1-Monats- und 10-Jahres-Sterblichkeit beobachtet [31].

Der vorteilhafte Effekt von Übergewicht und Adipositas auf die klinische Prognose bei chronischen Erkrankungen wurde bereits für CHI [32] und KHK [33], chronisch obstruktive Lungenerkrankung (COPD) [34] und chronische Niereninsuffizienz (CKD) [35] gezeigt. Dieses Phänomen wird als „Obesity Paradox“ [36] oder im Fall vom Schlaganfall als „Obesity-Stroke Paradox“ [37] bezeichnet.

1.3 Metabolische Komplikationen nach Schlaganfall

Neben Übergewicht, Adipositas und neurologischen Defiziten können auch weitere nicht-neurologische Komplikationen wie z.B. metabolische Komorbiditäten den klinischen Verlauf und Prognose nach Schlaganfall beeinflussen. Metabolische Komorbiditäten werden durch die vegetative Dysregulation mit sympathischer Überaktivierung, neuroendokrine Dysregulation und katabole/anabole Dysbalance charakterisiert. Nach Schlaganfall kann die autonome Dysfunktion auftreten und verschiedene Komplikationen inklusive endotheliale Dysfunktion, VHF, Hypertonie oder Insulinresistenz nach sich ziehen [38]. Die Regulationsstörungen des autonomen Nervensystems (ANS) kann man anhand der veränderten Parameter der Herzratenvariabilität (HRV) nachweisen [39]. Bei Patienten mit Schlaganfall wurde beobachtet, dass die verringerten Parameter der HRV unabhängig von anderen Faktoren mit höheren neurologischen Defiziten anhand der NIHSS Score und mRS Score assoziiert waren [40]. Die sympathische Überaktivierung kann außer der kardialen autonomen Dysregulation [40] auch eine zerebrale Dysregulation [41] verursachen.

Die pathophysiologischen Mechanismen die zu vegetativer Dysregulation führen, sind nicht vollständig bekannt. Eine akute Stressreaktion des Körpers ist mit einem erhöhten Spiegel von Katecholaminen und Kortisol im Zusammenhang mit erhöhter sympathischer Aktivierung verbunden. Die Folge ist eine katabolen Überaktivierung mit verminderter Nahrungsaufnahme, erhöhtem Proteinabbau und negativer Stickstoffbilanz [43,42]. Klinisch äußert sich die metabolische Dysregulation am häufigsten als ungewollter Verlust vom Körpergewicht, Muskel- und Fettgewebe [43].

Die systemische Inflammation mit erhöhtem Spiegel von proinflammtorischen Zytokinen (Interleukin 6, IL-6, Tumornekrosefaktor alfa, TNF-α, etc.) ist eine weitere Komplikation nach Schlaganfall [44,45], die wiederum Komorbiditäten wie endotheliale Dysfunktion [46] oder Eisenmangel [47] hervorrufen kann. Auch die Infektion von Harnwegen [48] oder Pneumonien [49] als Folge der Immunsuppression treten häufig nach Schlaganfall auf. Die Parameter der HRV haben sich prädiktiv für die Entwicklung der Infektionen nach Schlaganfall gezeigt [50].

1.3.2 Körpergewichtsveränderungen

Ungünstige Körpergewichtsveränderungen sind die häufigsten Komplikationen nach Schlaganfall. Vor allem ist Gewichtsverlust mit schlechter Prognose assoziiert. Zwei Studien zeigten ein Zusammenhang zwischen Gewichtsverlust von mindestens drei Kilogramm und erhöhter Mortalität bzw. erhöhtem Mortalitätsrisiko nach Schlaganfall [2,51]. Auch Übergewicht und Adipositas zum Zeitpunkt des Schlaganfalles hatten kein Vorteil auf das Mortalitätsrisiko nach 16 Monaten bei Patienten mit einem Gewichtsverlust von über drei Kilogramm [51]. Im Gegensatz war eine Gewichtszunahme von mehr als 5% des Ausgangsgewichts im Vergleich zu keiner Gewichtsveränderung tendenziell mit besserem Überleben verbunden [51]. Auch ein Untergewicht (BMI <18,5 kg/m²) ist mit schlechterer Prognose nach Schlaganfall assoziiert. Die Feed or Ordinary Diet (FOOD)-Studie zeigte, dass die untergewichtigen Patienten häufiger Komplikationen wie Lungenentzündungen, Infektionen oder gastrointestinale Blutungen entwickelten, was mit reduziertem klinischen Status und verringertem Überleben assoziiert war [52].

Ein Gewichtsverlust nach Schlaganfall wurde auch in tierexperimentellen Studien gezeigt. Bei Untersuchungen am Tiermodell des experimentell-induzierten Schlaganfalls im Bereich der mittleren Hirnarterie (middle cerebral artery occlusion, MCAO) wurde ein Gewichtsverlust von 20% nach Schlaganfall beobachtet [53]. Eine weitere experimentelle Studie zeigte eine Gewichtsabnahme des Herzmuskels nach MCAO. Es wurde eine Verringerung der Querschnittsdurchmesser von Kardiomyozyten festgestellt, der sich zwei Wochen nach der ischämischen Hirnschädigung nur teilweise wiederherstellte [54].

1.3.3 Kachexie als Ausdruck des katabolen Stoffwechsels

Während das „Obesity-Paradox“ einen positiven Effekt auf das Überleben und Prognose von Patienten mit chronischen Erkrankungen zeigt, hat ein Körpergewichtverlust einen negativen Effekt. Eine der bedeutendsten klinischen Manifestationen des katabolen Zustands ist ein Verlust des Körpergewichtes oder Kachexie, die mit dem Gewebeschwund aller drei Kompartimente (Fett-, Muskel- und Knochengewebe) einhergeht. Kachexie ist eine schwerwiegende Komplikation, die eine Reihe von chronischen Erkrankungen wie COPD [55], CHI [56], CKD oder onkologische Erkrankungen

[57] begleiten kann. Die Prävalenz einer Kachexie liegt zwischen 5% und 15% bei CHI und kann bis zu 80% bei fortgeschrittener onkologischer Erkrankung betragen [58,59]. Das Auftreten einer Kachexie ist mit ungünstiger klinischer Prognose und hoher Sterblichkeit assoziiert.

Der Begriff „Kachexie“ stammt aus dem Altgriechischen und bedeutet „schlechter Zustand“ [60]. Gemäß der Konsensdefinition ist Kachexie ein komplexes metabolisches Syndrom in Verbindung mit einer zugrundeliegenden chronischen Erkrankung, die durch Gewebeschwund gekennzeichnet ist [61]. Für die Diagnose einer Kachexie müssen neben einem Körpergewichtsverlust von mindestens 5% innerhalb der letzten 12 Monate oder kürzer, mehrere Kriterien zutreffen. Zu diesen Kriterien zählen eine verminderte Muskelkraft, Müdigkeit, Anorexie oder auffällige biochemischen Parameter wie erhöhte Entzündungsmarker (C-reaktives Protein (CrP), IL-6) oder niedriges Serumalbumin (Tabelle 3) [61].

Tabelle 3. Diagnostische Kriterien der Kachexie [60].

Gewichtsverlust von mindestens 5% in 12 Monaten oder kürzer bei bestehender zugrundeliegender Erkrankung oder Body Mass Index <20.0 kg/m²	
Plus 3 der folgenden Kriterien:	
Verminderte Muskelkraft (unteres Tertial)	**Abnormale Laborwerte:**
Schwäche[a]	Anämie: Hämoglobin <12 g/dl
Niedriger Index für die fettfreie Masse[b,c]	Inflammationsmarker:
Appetitmangel[d]	CrP*>5.0 mg/l, IL-6** >4.0 pg/ml
	Niedriges Serumalbumin: <3.2 g/dl

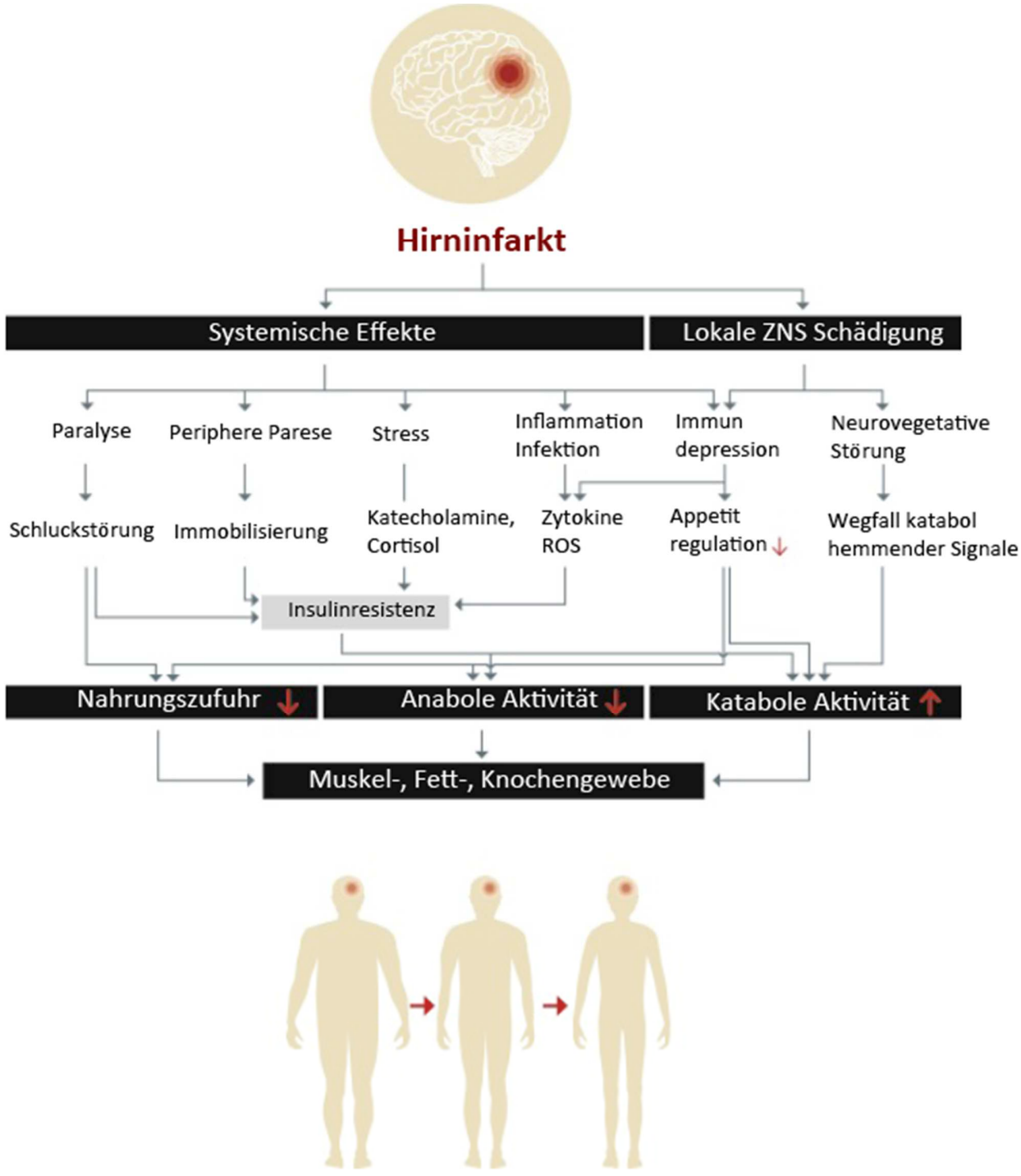
*CrP=C-reaktives Protein; **IL-6= Interleukin 6

[a]Schwäche: physische und/oder mentale Schwäche infolge einer Erkrankung mit einer Unfähigkeit die Alltagsbelastung mit gleicher Intensität fortzusetzen; [b]Ödemfrei; [c]Verminderung des Stützgewebes (z.B. mittiger Umfang des Oberarmmuskels <10. Perzentile gemäß Alter und Geschlecht; appendikulärer Skelettmuskel-Index, ASMI (kg/m^2) <5,45 bei Frauen und <7,25 bei Männern, gemessen mittels DEXA-Scan; [d]Begrenzte Nahrungsaufnahme (z.B. eine Aufnahme einer Gesamtkalorienmenge von <20 kcal/kg Körpergewicht/Tag; oder <70% der gewöhnlichen Nahrungsmenge oder Appetitmangel) [61].

1.3.4 Rolle der Kachexie nach Schlaganfall

Während die Kachexie bei vielen chronischen Erkrankungen im fortgeschrittenen Stadium als eine prognoserelevante Komorbidität auftritt, ist bei Patienten mit Schlaganfall unklar, welche Rolle die Kachexie beim Schlaganfall spielt. Die klinische Evidenz deutet darauf hin, dass die metabolische Dysregulation nach Schlaganfall häufig vorkommt. Klinisch kann sich die metabolische Dysregulation als einer Vielfalt von den oben beschriebenen Symptomen äußern. Ungewollter Verlust vom Körpergewicht ist für Schlaganfall prognostisch relevant. Daher ist unsere Hypothese, dass Gewichtsverlust bei Patienten mit Schlaganfall aufgrund von Gewebeschwund und Veränderung der Körperzusammensetzung als Folge eines allgemeinen katabolen / anabolen Ungleichgewichts auftritt. Die Gehirnschädigung geht mit einer massiven Aktivierung inflammatorischer und hormonaler Kaskaden einher, was zur Entstehung der vegetativen Dysregulation des katabolen/anabolen Ungleichgewichtes führt. Somit kann der Gewichtsverlust nach Schlaganfall ein Ausdruck einer katabolen Stoffwechsellage sein, zudem zusätzliche Faktoren wie z.B. Immobilisierung und erschwerte Nahrungsaufnahme aufgrund von Schluckstörungen deutlich beitragen können (Abbildung 1).

Abbildung 1. Zusammenfassung der pathophysiologischen Mechanismen zum Gewichtsverlust nach Schlaganfall. *Modifiziert aus Scherbakov, N., Döhner, W. Buchkapitel: Komplikationen und Folgeerkrankungen nach Schlaganfall; Thieme, 2015 [42].*



1.3.5 Sarkopenie – neuer Code, alte Krankheit

Die Muskelmasse erreicht ihren höchsten Wert in der dritten bis vierten Lebensdekade. Nach der fünften Lebensdekade beginnt ihre kontinuierliche Verringerung [62,63]. Das Phänomen vom Skelettmuskelmasseverlust in Assoziation mit Altern ist lange bekannt und wurde bereits in 30er Jahren des 20. Jahrhundert vom Neurologen M. Critchle beschrieben [64,65]. Der altersbedingte physiologische Verlust von Skelettmuskelmasse wurde in den 90er Jahren des letzten Jahrhunderts von Prof. Rosenberg als Sarkopenie bezeichnet [66], was aus dem Griechischen wörtlich übersetzt „Mangel an Fleisch" bedeutet. Sarkopenie ist definiert als ein Skelettmuskelmasse Index (SMMI) von mindestens zwei Standardabweichungen unter dem Mittelwert einer gesunden jungen Referenzgruppe zwischen 20 und 30 Jahren gleichen Geschlechts und gleichen ethnischen Hintergrunds [67].
Jedoch kann eine Sarkopenie auch sekundär im Zusammenhang mit chronischen Erkrankungen wie CHI [68], CKD [69], COPD [70,71] oder Krebs [72] als eine schwere Komorbidität auftreten. Im diesen Fall, wird der Fokus bei der Diagnosestellung auf Skelettmuskelabbau und nicht auf die Funktion gelegt [73]. Zusätzlich zum Muskellabbau werden eine systemische Entzündung und häufig auch ein Gewichtsverlust nachgewiesen. Ob die sekundäre Sarkopenie als Vorstufe der Kachexie verstanden werden kann bleibt umstritten [74]. 2016 wurde die Sarkopenie in der Internationalen statistischen Klassifikation der Krankheiten ICD-10 unter dem Code M62.84 verschlüsselt [75].

1.3.5.1 Sarkopenie nach Schlaganfall und ihre metabolischen Besonderheiten

Nach Schlaganfall sind körperliche Behinderungen aufgrund der motorischen Störungen (Muskellähmungen, Spastizität) die häufigsten akuten und chronischen Komplikationen. Ca. 50% der Patienten verbleiben mit Hemiparesen und ca. 30% der Patienten können nicht frei gehen und benötigen eine Unterstützung [76]. Die Patienten weisen eine reduzierte Muskelkraft und Muskelverminderung auf [3,4], die auf verschiede Ursachen wie systemische Inflammation oder Muskellähmungen zurückzuführen ist. Die Signalunterbrechung aufgrund der Hirnischämie und Schädigung des sensomotorischen Netzwerkes zwischen den oberen motorischen Nervenbahnen und Muskel führt zur Reduktion der neuronalen Stimulation des Skelettmuskels. Bereits vier

Stunden nach einem Hirninfarkt kann man eine Abnahme der motorischen Einheiten (the motor unit number estimate, MUNE) beobachten, was zur verringerten Erregbarkeit des spinalen Motoneurons führt [77]. Durch den Abbau motorischer Endplatten [78] kommt es zur Denervierung des Skelettmuskels [79,43], und zur Verringerung der Muskelkraft [80] und später der Muskelmasse [78,79]. Im späteren Verlauf wird auch der Muskelphänotyp verändert [81].

Im Vergleich zur altersabhängigen Sarkopenie weist die schlaganfallassoziierte Sarkopenie sowohl phänotypische Veränderungen als auch metabolische Besonderheiten auf. Diese äußern sich in einer Erhöhung der lypolytischen und glykolytischen Aktivität der Muskelzellen, und somit einer Veränderung des oxidativen Stoffwechsels [82]. Charakteristisch für den paretischen Skelettmuskel ist eine Verschiebung des Verhältnisses zwischen den Muskelfasern mit Prädominanz von schnell-zuckenden Fasern vom Myosin Heavy Chain (MHC) Typ II. Die Muskelfasern vom Typ II haben einen anaeroben also glykolytischen Stoffwechsel was als Folge zu einem hohen Verbrauch von Adenosintriphosphat (ATP) führt. Allerdings wurde bei Patienten im Subakutstadium eine Insulinresistenz in beiden, paretischen und nicht-paretischen Extremitäten festgestellt, was auf einen systemischen Charakter der metabolischen Störungen nach Schlaganfall hindeutet [82]. Daher wurde der Begriff der schlaganfallassoziierten Sarkopenie geprägt [83,43].

1.3.5.2 Assessment der Körperzusammensetzung

Bei Sarkopenie und Kachexie verändert sich die Körperzusammensetzung. Die Körperzusammensetzung kann man mit Hilfe verschiedener diagnostischer Verfahren wie DEXA-Untersuchungen (Duale X-Ray Absorptiometrie) [84], Magnetresonanztomographie (MRT), Computertomographie (CT), Ultraschall [85] oder anthropometrischen Messmethoden festgestellt werden. Die DEXA-Analysen gehören zum „Goldstandard“ im Vergleich zu Anatomie-basierten bildgebenden Verfahren und erlauben eine genaue Messung der Magermasse und des Fettgewebes vor allem der oberen und unteren Extremitäten. Anhand der Magermassemessungen der Extremitäten wird ein appendikulärer Skelettmuskel-Index (ASMI) bestimmt, der im weiteren zur Diagnose der Sarkopenie verwendet wird [61]. Da die DEXA-Messungen mit einer Röntgenbestrahlung und relativ hohem Zeitaufwand (Gesamtkörperscan 5-6 Minuten/Patient, Platzierung des Patienten, Einstellung am Gerät etc.) verbunden sind, wird diese Methode in der

Indikation zur Bestimmung der Körpergewebezusammensetzung vor allem im Rahmen der klinischen Studien und nicht in der klinischen Routine angewendet. Die bioelektrische Impedanz (BIA) ist eine weitere Methode der Körpergewebebestimmung. Diese Methode korreliert mit sehr hoher Genauigkeit mit DEXA-Messungen, ist mit keiner Röntgenstrahlung verbunden und kann am Krankenbett durchgeführt werden [86]. Allerdings sollten die Messungen bei Ödem-freien Patienten durchgeführt werden; BIA-Untersuchungen sind bei Patienten mit Herzschrittmachern kontraindiziert.

1.3.5.3 Bestimmung der Muskelmasse

Ein Assessment der Muskelmasse mittels Biomarker könnte bei der Diagnosestellung der Sarkopenie hilfreich sein. Das Fragment vom Agrin-Protein, CAF22, wurde als Marker des Muskelschwundes vorgeschlagen [87] und bereits bei Herzinsuffizienz [88] und bei altersabhängiger Sarkopenie [89,90] getestet. Das Protein Agrin ist 225 kDa schwer; es wird von den Neuronen in den synaptischen Spalt der neuromuskulären Synapsen sezerniert und ist für die Organisation der Acetylcholin (ACh)-Rezeptoren in der postsynaptischen Membran zuständig [106,107]. Beim Muskelschwund wird Agrin durch die Neuropeptidase Neurotrypsin vermehrt gespaltet und sein Fragment, CAF22, kann nachgewiesen werden. CAF22 als Marker der Muskelabbau wurde bei Patienten mit Herzinsuffizienz und mit altersbedingter Sarkopenie getestet. Inwiefern der CAF22 als diagnostischer Marker des Muskelschwundes beim Schlaganfall verwendet werden kann, war bisher nicht bekannt.

1.3.6 Vegetative Dysregulatoin

Gewichtsverlust nach Schlaganfall ist eine schwerwiegende Komplikation, die auf metabolischen Ungleichgewicht hindeuten könnte. Aber auch weitere Krankheitsbilder können auf die vegetative Dysregulation hindeuten. Dazu gehören u.a. endotheliale Dysfunktion und atembezogene Schlafstörungen.

1.3.6.1 Endotheliale Dysfunktion

Eine Funktionsstörung des Endothels die mit gestörter Gefäßdilatation, Adhäsion von Leukozyten und Thrombozyten, zunehmender Gefäßpermeabilität und vermehrtem Wachstum Gefäßmuskelzellen einhergeht, wird als endotheliale Dysfunktion (ED) bezeichnet [91]. Periphere ED gilt als Ausdruck des metabolischen Ungleichgewichtes und ist für die Pathogenese der kardiovaskulären und zerebrovaskulären Erkrankungen einschließlich Schlaganfall relevant [7,92]. Die ED ist ein Prädiktor für kardiovaskuläre Mortalität. Die ED erhöht das Risiko einer Minderdurchblutung peripherer Organe und des Gehirnes und steigert damit das Potenzial für die Entwicklung eines Schlaganfalls [93,94]. Das Risiko für ischämischen Schlaganfall wird durch die periphere ED dreifach erhöht [95]. Es gibt Unterschiede in der Prävalenz der ED zwischen den Subtypen des Schlaganfalls; die Patienten mit Schlaganfall vom lakunären, makroangiopathischen und kardioembolischen Subtyp sind am meisten betroffen [7,96]. Die ED kann auch Ursache für eine verminderte Muskelkraft, Ausdauer und schnelle Müdigkeit sein [97,98] und den funktionellen Status nach Schlaganfall negativ beeinflussen.

1.3.6.2 Schlafbezogene Atemstörungen

Schlafbezogene Atemstörungen (sleep-disordered breathing, SDB) gehören gleichzeitig zu den Ursachen als auch zu den Folgen des Schlaganfalls [99,100]. SDB kann viele Komplikationen wie z.B. wiederkehrende hypoxische bzw. hyperkapnische Episoden, Störungen des Säure-Basen Haushaltes, Mangel an erholsamen Schlaf oder eine Dysregulation des autonomen Nervensystems verursachen [101]. Störungen des zirkadianen Rhythmus können zur strukturellen und elektrophysiologischen Veränderungen am Herzen und zu kardialen Arrhythmien führen [101]. Vor allem die obstruktive Schlafapnoe (OSA) ist mit erhöhtem Risiko von kardialen Arrhythmien verbunden [102]. In einer Studie wurden 400 Patienten mit Schlafapnoe 24 Stunden elektrokardiographisch untersucht. Bei diesen Patienten wurden nächtlichen Bradykardien oder Tachykardien festgestellt. Im Gegenteil, Patienten, die Schlafapnoe und eine Störung der vegetativen Regulation des Herzens wie z. B. nach Herztransplantation oder mit Shy-Drager-Syndrom hatten, konnten keine Herzrhythmusstörungen im 24-Stunden Elektrokardiogramm (EKG)

festgestellt werden [103]. Diese Ergebnisse geben einen Hinweis darauf, dass das autonomes Nervensystem und vegetative kardiale Kontrolle durch SDB beeinflusst werden kann. Die SDB kann zur sympathischen Überaktivierung durch die Beeinträchtigung der vagalen Kontrolle führen und damit eine Entwicklung der arteriellen Hypertonie und kardiometabolischen Störungen begünstigen [104].

1.4 Zielsetzung und Beitrag dieser Arbeit

Die vorliegende Arbeit widmet sich der Untersuchung der metabolischen Komorbiditäten und deren Auswirkung auf den klinischen Verlauf bei Patienten nach Schlaganfall. Das Ziel ist eine systemische Analyse der metabolischen Komorbiditäten als mögliche Ursache für eingeschränkte Lebensqualität und einen reduzierten körperlichen und funktionellen Zustand im Akutstadium, während der Frührehabilitation und im chronischen Verlauf nach Schlaganfall. Im Einzelnen werden untersucht:

- Körpergewichtsveränderungen und Auftreten von Kachexie bei Patienten im Akutstadium und ein Jahr nach Schlaganfall;
- die Wertigkeit des C-terminalen Agrin (CAF) Fragmentes als eines Parameters des Muskelschwundes bei Patienten mit akutem Schlaganfall und während der stationären Frührehabilitation;
- Eisenmangel und deren Auswirkung auf die Muskelkraft bei Patienten mit akuten und chronischen Schlaganfall;
- Herzratenvariabilität als Parameter der autonomen Regulation in Relation zum funktionellen Zustand vor und nach stationärer Frührehabilitation nach Schlaganfall;
- Atembezogene Schlafstörungen im Akutstadium nach Schlaganafall, die Beziehung zwischen diesen Schlafstörungen und der peripheren endothelilalen Dysfunktion, sowie deren Auswirkung auf den physischen und funktionellen Zustand ein Jahr nach Schlaganfall.

2. Eigene Arbeiten

2.1 Gewichtsveränderungen und Inzidenz von Kachexie nach dem Schlaganfall

Scherbakov N, *Pietrock C, Sandek A, Ebner N, Valentova M, Springer J, Schefold JC, von Haehling S, Anker SD, Norman K, Haeusler KG, Doehner W. Body weight changes and incidence of cachexia after stroke. J Cachexia Sarcopenia Muscle. 2019; 10:611-620.*

Der klinische Verlauf nach Schlaganfall hängt nicht nur vom Schweregrad der neurologischen Defizite, sondern auch von metabolischen Komorbiditäten ab. Die klinischen Studien zeigten eine direkte Beziehung zwischen hohem BMI, einem besseren Ernährungsstatus und günstiger Prognose nach Schlaganfall [105]. In der vorliegenden prospektiven Beobachtungsstudie untersuchten wir die Gewichtsveränderungen, Inzidenz einer Kachexie und klinische Prognose von Patienten nach Schlaganfall.

Insgesamt wurden 67 Patienten (69 ± 11 Jahre, BMI 27,0 ± 4,1 kg/m², 42% Frauen) eingeschlossen. Die Studienuntersuchungen fanden bei Baseline, BL (4 ± 2 Tage) und bei 1 Jahr Follow-up,1yFU (389 ± 26 Tage nach Schlaganfall) statt. Die Körpergewebezusammensetzung wurde mittels Dual- DEXA analysiert, der funktionelle Status wurde mittels BI und mRS gemessen. Kachexie wurde definiert durch einen Gewichtsverlust ≥5% in einem Jahr und zusätzliche klinische Parameter.

Bei 1yFU zeigten 63% der Patienten eine Gewichtszunahme oder stabiles Gewicht, 16% eine geringe Gewichtsabnahme (< 5%) und 21% der Patienten wurden kachektisch. Kachektischen Patienten verloren 19% der Fettmasse und 6,5% der Magermasse im Gegensatz zu Patienten mit geringer Gewichtsabnahme, die keine Magermasse verloren haben. Zudem hatten die kachektischen Patienten eine 34% geringere Muskelkraft (21,9 ± 13,0 kg, $P < 0.05$) und einen niedrigeren funktionellen Status (48% höhere mRS 2,1 ± 1,6, $P < 0,05$ sowie 21% niedrigeren BI 71 ± 39, $P< <0,01$) im Vergleich zu nicht kachektischen Patienten. Der schlechte funktionelle Status war mit niedriger Magermasse und Kachexie assoziiert.

Diese Studie zeigte, dass jeder fünfte Patient ein Jahr nach Schlaganfall kachektisch wurde. Kachektische Patienten hatten einen schlechteren funktionellen Status und niedrigere Muskelmasse.

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Body weight changes and incidence of cachexia after stroke

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Abstract

Background Body weight loss is a frequent complication after stroke, and its adverse effect on clinical outcome has been shown in several clinical trials. The purpose of this prospective longitudinal single-centre observational study was to investigate dynamical changes of body composition and body weight after ischemic stroke and an association with functional outcome.

Methods Sixty-seven consecutive patients (age 69 ± 11 years, body mass index 27.0 ± 4.1 kg/m^2, 42% female patient, mean ± SD) with acute ischemic stroke with mild to moderate neurological deficit (National Institute of Health Stroke Scale median 4, ranged 0–12) were analysed in the acute phase (4 ± 2 days) and at 12 months (389 ± 26 days) follow-up. Body composition was examined by dual energy X-ray absorptiometry. Cachexia was defined according to the consensus definition by body weight loss ≥5% within 1 year and additional clinical signs. Lean tissue wasting was considered if a ratio of upper and lower limbs lean mass sum to squared height (kg/m^2) was ≤5.45 kg/m^2 for female patient and ≤7.25 kg/m^2 for male patient.

Results According to the body weight changes after 12 months, 42 (63%) patients had weight gain or stable weight, 11 (16%) patients had moderate weight loss, and 14 (21%) patients became cachectic. A relative decline of 19% of fat tissue and 6.5% of lean tissue was observed in cachectic patients, while no changes of lean tissue were observed in non-cachectic patients after 12 months. The modified Rankin Scale was 48% higher (2.1 ± 1.6, $P < 0.05$), Barthel Index was 22% lower (71 ± 39, $P < 0.01$), and handgrip strength was 34% lower (21.9 ± 13.0, $P < 0.05$) in cachectic compared to non-cachectic patients after 12 months. The low physical performance if defined by Barthel Index <60 points was linked to the lean tissue wasting (OR 44.8, $P < 0.01$), presence of cachexia (OR 20.8, $P < 0.01$), and low body mass index <25 kg/m^2 (OR 11.5, $P < 0.05$). After adjustment for co-founders, lean tissue wasting remained independently associated with the low physical performance at 12 months follow-up (OR 137.9, $P < 0.05$).

Conclusions In this cohort study, every fifth patient with ischemic stroke fulfilled the criteria of cachexia within 12 months after index event. The incidence of cachexia was 21%. Cachectic patients showed the lowest functional and physical capacity.

Keywords Body weight; Body composition; DXA; Stroke; Cachexia

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Introduction

Stroke is a leading medical, socio-economic and health care problem worldwide. Increasing global life expectancy and a reduction of the acute post-stroke mortality rate contribute to the rising costs in stroke care.[1–3] About two thirds of the patients remain disabled after stroke.[4,5] The course of post-stroke recovery depends on the initial stroke severity and stroke-related complications including inflammation, infection, metabolic dysfunction, and degree of disability. Several clinical trials have shown an important role of body weight and nutritional status at stroke onset for the functional outcome and mortality after stroke[6–8] and an association between the body weight and mortality in experimental stroke.[9]

Body weight loss after stroke is a common observation in acute and chronic stroke.[6] However, detailed information on body composition changes after stroke are scarce.[10,11] Standardized assessment of body composition is feasible using dual-energy X-ray absorptiometry (DXA), bioelectrical impedance, or computer tomography.[12–14] Tissue wasting or cachexia is a complex metabolic syndrome of multifactorial origin[15] that has been most frequently shown in association with several chronical diseases including chronic heart failure, chronic obstructive pulmonary disease, kidney disease, or cancer.[16–19] The reported prevalence of cachexia ranges between 5% and 80% depending on disease and disease severity and has been linked to poor outcome.[20,21] However, the incidence of cachexia has not been studied in detail in patients with ischemic stroke.

The aim of this prospective observational study was to analyse changes of body weight and body composition and to investigate the functional outcome in cachectic and non-cachectic patients with stroke.

Methods

Ethical conduct and study population

The investigator-initiated single-centre longitudinal prospective observational body size in stroke study[22] (German registry for clinical trials number DRKS00000514) was approved by the Ethic Committee of Charité-Universitätsmedizin Berlin, Germany (EA2/008/09), and written informed consent was obtained from all patients.

We studied 67 patients with acute ischemic stroke within the territory of the middle cerebral artery. The patients with mild to moderate neurological deficit [defined by the National Institute of Health Stroke Scale (NIHSS) ≤12 points] were consecutively enrolled within 48 h after stroke onset while being admitted to a stroke unit (Department of Neurology, Charité-Universitätsmedizin Berlin, Campus Virchow-Klinikum, Berlin, Germany) from June 2009 to November 2012. Following the discharge from the stroke unit, 34 patients were admitted to post-stroke rehabilitation. These patients underwent adjusted early post-stroke rehabilitation programs in specialized rehabilitative clinics according to national standards for rehabilitation procedures after stroke.

Study related examinations included assessments of body composition, physical and functional capacity, muscle strength, and nutritional status and were completed in hospital at baseline (4 ± 2 days after the index event) and at 12 months follow-up (389 ± 26 days after stroke onset) visit. According to the changes of the body weight after 12 months, patients were retrospectively grouped into (i) weight gain/stable weight, (ii) moderate weight loss (<5% of body weight), and (iii) cachectic subgroups. Cachexia was defined by weight loss ≥5% of the original weight over a period of 12 months and at least three clinical criteria according to the current consensus definition.[15]

Assessment of functional outcome and muscle strength after stroke

Functional capacity and degree of disability were assessed by the Barthel Index (BI) and by the modified Rankin Scale (mRS).[23] The BI contains 10 basic activities of the daily living related to self-care and mobility with scores of '0' to '100', where the lower scores indicate greater dependency. Low functional status was defined by the BI <60 points.

The mRS measures physical independency by assessment of the body function, activity, and participation in daily tasks on the scale ranging from '0' (no symptoms) to '6' (death). Isometric muscle strength of the hand was assessed by the handgrip strength test using a handgrip dynamometer (Saehan Corporation, Korea). The highest of three handgrip measurements of the non-paretic hand was used for analyses.

Maximal isometric muscle strength of the quadriceps muscle (expressed in Newton, N) was measured as described previously.[24] Briefly, the freely hanging legs of the sitting patients were connected at the ankle with a pressure transducer (Multitrace 2, Lectromed, Jersey, Channel Islands), and maximal isometric strength was assessed from the best of three contractions on each leg, with a resting period of at least 60 s in between.

Body composition

Body mass index (BMI) was calculated as a ratio of body weight and squared height (kg/m^2). For detailed body composition assessment, dual-energy DXA was performed using LunarProdigy densitometer (GE Healthcare, Chalfont St. Giles, UK). Total body scans were analysed to obtain total and regional (upper and lower limbs, and trunk) measurements

of the fat and lean tissue. The sum of the lean or fat mass of the upper and lower limbs was termed as an appendicular muscle mass (ALM) or appendicular fat mass. The fat-free mass index (FFMI) was calculated as a ratio of ALM and squared height (kg/m^2). Lean tissue wasting was defined by low FFMI (for female patient ≤5.45 kg/m^2 and for male patient ≤7.25 kg/m).

Appetite was assessed according to the visual analogue scale ranging from '0' (no appetite) to '10' (very good appetite).[25] In addition, nutritional status was assessed by Mini Nutritional Assessment at 12 months as follows: patients were undernourished, if they achieved 16 points or less, at risk for malnutrition if they achieved 17–23.5 points, or had a normal nutritional status if they achieved ≥24 points.[26]

None of the patients included in our study had dysphagia on a clinical relevant level (preventing oral feeding), and none was fed enterally or parenterally.

Blood sampling

Venous blood samples were obtained in all patients after 12 h of overnight fasting. Standard biochemical parameters were assessed by routine laboratory measurement. Systemic inflammation was present if C-reactive protein (CRP) plasma level was over 6.1 mg/dL, as defined previously.[27]

Statistical analysis

All data were presented as means ± standard deviation, median (interquartile range), or percentage as appropriate. All variables were tested for normal distribution using the Kolmogorov–Smirnov test. Non-normally distributed data were log transformed to achieve a normal distribution where indicated. Statistical comparisons were made using paired or unpaired Student's *t*-tests as appropriate, analysis of variance followed by Fisher's *post hoc* test, Mann–Whitney, or Kruskal–Wallis test. Chi-squared test was used to assess categorical distribution between the groups. Pearson's simple regression and logistic regression were used as appropriate. A value of $P < 0.05$ was considered statistically significant. Statistical analyses were performed with the StatView 5.0 software package (SAS Institute Inc, Cary, NC) and the software GraphPad Prism 6.0.

Results

Baseline clinical characteristics of the patients and retrospective study subgroups are presented in *Table* 1. Twelve months after stroke, 42 (63%) patients had stable weight or weight gain, 11 (16%) of all patients were found with moderate weight loss, and 14 (21%) patients became cachectic (*Figure 1*). There were no significant differences regarding the BMI, the side of stroke-related brain damage, thrombolytic therapy, frequency of paresis, or admission to post-stroke rehabilitation at baseline between all subgroups. Patients who became cachectic 12 months after stroke were significantly older ($P < 0.05$), had more frequently advanced neurological deficit with NIHSS ≥5 (64%, $P < 0.05$), had higher degree of dependence by mRS ($P < 0.01$) and BI ($P < 0.05$), and had the lowest albumin and the highest CRP serum levels ($P < 0.001$ and $P < 0.01$, respectively) at baseline compared to other subgroups (*Table* 1).

According to univariate regression analysis, baseline parameters including age, neurological deficit as indicated by a NIHSS ≥5 points, functional dependency as indicated by mRS and BI, albumin and log-transformed CRP serum levels, systemic inflammation as defined by CRP serum levels >6.1 mg/dL, self-reported appetite, and handgrip strength were associated with cachexia onset (*Table* 2). After adjustment for age, sex and BMI, systemic inflammation, and CRP serum levels were independently associated with cachexia development (*Table* 2).

Body composition

At baseline, no differences in body composition were observed among study subgroups (*Table* 3). While in the stable weight/weight gain group no loss of lean mass after 12 months was observed, patients with weight loss showed a reduction in lean mass (*Table* 3). Thus, in patients who became cachectic, a significant reduction of ALM by 6.5% ($P < 0.05$) was observed (*Table* 3). The frequency of the lean tissue wasting as defined by FFMI ≤5.45 kg/m^2 for female patient and FFMI ≤7.25 kg/m^2 for male patient in the cachectic subgroup was 43% after 12 months ($P < 0.001$) vs. baseline. In addition, appendicular fat mass 12 months after stroke was also the lowest in cachectic patients ($P < 0.05$).

In the stable weight/weight gain group and the moderate weight loss group, no significant reduction of lean tissue according to the FFMI was observed (*Table* 3). Lean tissue wasting showed no relation to paresis in the studied patients, (OR 1.1, 95% CI [0.12–10.6], $P = 0.9$).

Functional outcome at 12 months follow-up

Clinical characteristics of the patient subgroups at 12 months follow-up are shown in *Table S1*. Twelve months after stroke an improvement of functional capacity compared to baseline was found in most patients with stroke (*Figure 2A* and *2B*). This improvement applied to patients with and without cachexia. Nonetheless, cachectic patients

Table 1. Clinical characteristics of study cohort at baseline

Parameter	Study group $n = 67$	Weight gain/stable weight $n = 42$	Moderate weight loss $n = 11$	Cachexia $n = 14$	*P*-value
Age, years	69 ± 11	66 ± 11	70 ± 10	75 ± 9	0.03
Male sex; % (*n*)	58 (39)	60 (25)	82 (9)	36 (5)	0.07
Body mass index, kg/m^2	27.0 ± 4.1	26.5 ± 3.7	28.7 ± 5.1	26.4 ± 4.8	0.3
Body mass index <25 kg/m^2; % (*n*)	30 (20)	31 (13)	18 (2)	36 (5)	0.6
Systolic RR, mmHg	138 ± 24	136 ± 21	150 ± 27	138 ± 30	0.2
Diastolic RR, mmHg	77 ± 13	77 ± 12	82 ± 14	73 ± 14	0.1
Mean RR, mmHg	97 ± 15	96 ± 14	105 ± 17	94 ± 14	0.2
Stroke severity					
Thrombolysis with rt-PA; % (*n*)	31 (21)	29 (12)	27 (3)	43 (6)	0.6
Right hemispheric stroke; % (*n*)	66 (42)	60 (25)	73 (8)	75 (9)	0.7
Paresis; % (*n*)	84 (56)	86 (36)	82 (9)	79 (11)	0.8
Post-stroke rehabilitation; % (*n*)	51 (34)	52 (22)	46 (5)	50 (7)	0.9
NIHSS score	4.5 ± 3.2	4.3 ± 3.2	3.5 ± 2.7	5.8 ± 3.0	0.2
NIHSS score 5–12; % (*n*)	37 (25)	33 (14)	18 (2)	64 (9)	0.02
Modified Rankin Scale score	2.0 ± 1.3	1.8 ± 1.1	1.6 ± 1.0	3.0 ± 1.4	0.003
Modified Rankin Scale score 4–5; % (*n*)	18 (12)	12 (5)	9 (1)	43 (6)	0.02
Barthel Index score	78 ± 29	82 ± 26	88 ± 20	60 ± 38	0.03
Barthel Index score < 60	27 (18)	21 (9)	12 (2)	50 (7)	0.09
Comorbidities					
Diabetes mellitus; % (*n*)	27 (18)	17 (7)	55 (6)	36 (5)	0.03
Hypertension; % (*n*)	84 (56)	83 (35)	82 (9)	86 (12)	0.9
Dyslipidemia; % (*n*)	59 (39)	55 (23)	82 (9)	50 (7)	0.2
Biochemistry					
Haemoglobin, g/dL	14 ± 2.0	14.0 ± 1.9	14.5 ± 1.1	13.6 ± 2.7	0.5
Albumin, g/L	36.8 ± 5.6	37.4 ± 5.9	39.1 ± 3.3	32.2 ± 5.9	0.001
Glucose, mg/dL	115 ± 44	114 ± 46	136 ± 45	100 ± 24	0.2
HbA1c, %	6.2 ± 1.4	6.0 ± 1.2	6.7 ± 1.5	6.4 ± 1.8	0.2
Sodium, mmol/L	140 ± 4	141 ± 3	139 ± 6	141 ± 4	0.6
Potassium, mmol/L	4.1 ± 0.4	4.1 ± 0.3	4.0 ± 0.5	4.0 ± 0.5	0.9
Triglyceride, mg/dL	151 ± 71	154 ± 75	142 ± 43	156 ± 81	0.7
Cholesterol, mg/dL	196 ± 44	198 ± 45	176 ± 49	203 ± 38	0.5
Low density lipoprotein, mg/dL	114 ± 42	113 ± 45	114 ± 37	128 ± 26	0.3
High density lipoprotein, mg/dL	51 ± 15	54 ± 17	50 ± 11	46 ± 14	0.2
Creatinine, mg/dL	1.0 ± 0.5	1.1 ± 0.5	1.1 ± 0.3	0.9 ± 0.2	0.8
C-reactive protein, mg/L	3.8 [1.8–6.3]	3.4 [1.7–6.6]	1.7 [1.0–4.8]	8.8 [4.6–22.4]	0.002
Uric acid, mg/dL	5.7 ± 1.4	5.6 ± 1.5	5.7 ± 1.3	5.9 ± 1.2	0.9

NIHSS, National Institute of Health Stroke Scale.

remained with the more severe disability as shown by the higher mRS score (2.1 ± 1.6, $P < 0.01$) and lower BI score (71 ± 39, $P < 0.01$) compared to other study subgroups (*Figure 2A* and *2B*). Better functional capacity according to the BI was associated with weight gain ($R = 0.25$, $P < 0.05$) in all patients with stroke (*Figure 2C*).

Cachectic patients showed the lowest muscle strength as assessed by handgrip strength test and quadriceps strength test (*Figure 3A* and *3B*). An association between the FFMI and handgrip strength was observed in non-cachectic ($R = 0.54$, $P < 0.0001$) and in cachectic ($R = 0.71$, $P < 0.01$) patients at 12 months follow-up (*Figure 3C*).

Univariate logistic regression analysis showed an association of low functional status as defined by BI score <60 points with the lean tissue wasting, presence of cachexia, BMI, body weight loss, nutritional status, low albumin, and high CRP serum levels (*Table* 4). After adjustment for covariates included age and sex, lean tissue wasting and FFMI remained independently associated with low functional status.

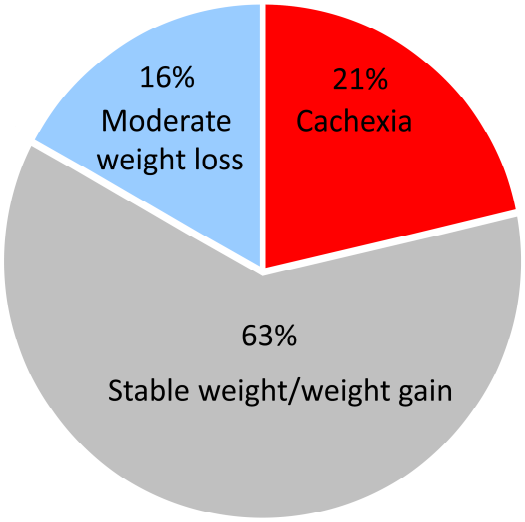
Nutritional status at 12 months follow-up

Significant improvement of the appetite according to the visual appetite scale was observed in patients with weight gain/stable weight but not in those with any degree of weight loss (*Figure 4A*). Cachectic patients were found with the lowest appetite and nutritional status (*Figure 4A* and *4B*). A direct association between the weight gain and appetite was observed ($R = 0.4$, $P < 0.002$, *Figure 4C*).

Systemic inflammation

At 12 months follow-up, inflammatory activity was still ongoing in cachectic patients [median CRP 7.6 (interquartile range 2.6–15.2) mg/dL, $P < 0.01$] compared to the other subgroups (Table S1). Lean tissue wasting, nutritional status, self-reported appetite, mRS, BI, and handgrip strength were associated with systemic inflammation (*Table* 5).

Figure 1 Body weight changes at 12 months follow-up in the study population. Incidence of cachexia.



Discussion

Our study demonstrates an incidence of cachexia of 21% within 1 year after stroke. Physical and functional clinical status at 12 months follow-up was lower in cachectic patents compared to non-cachectic patients with stroke. We also identified clinical parameters predictive for development of cachexia after stroke.

Tissue wasting

Using DXA analyses, we showed that patients with cachexia, in contrast to patients without cachexia, lost fat mass and lean tissue. Loss of lean mass in paretic patients with stroke, having sedentary lifestyle, is a common observation.[28–30] However, we observed a lean tissue depletion in cachectic patients regardless of the paresis. Previously, a stroke-related systemic lean tissue wasting due to catabolic activation was reported in a mouse model of middle cerebral artery occlusion.[9] The extent of the brain damage in mice correlated with apoptotic and proteolytic activity in skeletal muscle in both legs.[9] In line with this experimental data, we observed an association between the stroke severity and the presence of cachexia.

Certainly, lean tissue decline is an age-dependent phenomenon, with the prevalence ranging between 8% and 60% in healthy elders.[31–35] Previous study showed a prevalence of sarcopenia of 7% in chronic stroke survivors within 3 years after ischemic or haemorrhagic stroke.[10] In the present cohort, the prevalence of the lean tissue depletion at the time of the index stroke was within the generally observed age-dependent range. However, an increase from 6% to 13% in the prevalence of lean tissue depletion within 12 months with the highest proportion among cachectic patients (43%) might be linked to stroke-related metabolic imbalance.[36]

Systemic inflammation

An association between cachexia and inflammatory state in patients with chronic heart failure or chronic obstructive

Table 2. Baseline parameters associated with cachexia onset after stroke

Parameter	OR	95% CI	*P*-value
Presence of systemic inflammation	8.54	[2.27–32.17]	0.002
C-reactive protein, log[mg/L]	7.93	[1.99–31.60]	0.003
NIHSS 5–12 points	4.16	[1.20–14.39]	0.02
Barthel Index <60 points	3.80	[1.10–13.20]	0.03
Modified Rankin Scale, point	2.19	[1.32–3.65]	0.003
Age, year	1.08	[1.01–1.15]	0.02
Barthel Index, 10 points	0.78	[0.64–0.95]	0.02
Handgrip strength, kg	0.91	[0.85–0.98]	<0.01
Albumin, g/dL	0.79	[0.68–0.92]	0.002
Appetite, point VAS	0.51	[0.34–0.77]	0.002
Appendicular lean mass, kg	0.83	[0.70–0.99]	0.03
Lean mass upper limbs, kg	0.58	[0.34–0.99]	<0.05
Lean mass lower limbs, kg	0.76	[0.60–0.96]	0.02
Multivariable logistic model adjusted for age, sex, and BMI			
I. Systemic inflammation	9.66	[1.96–47.63]	0.005
II. C-reactive protein, log[mg/L]	6.67	[1.34–33.12]	0.02

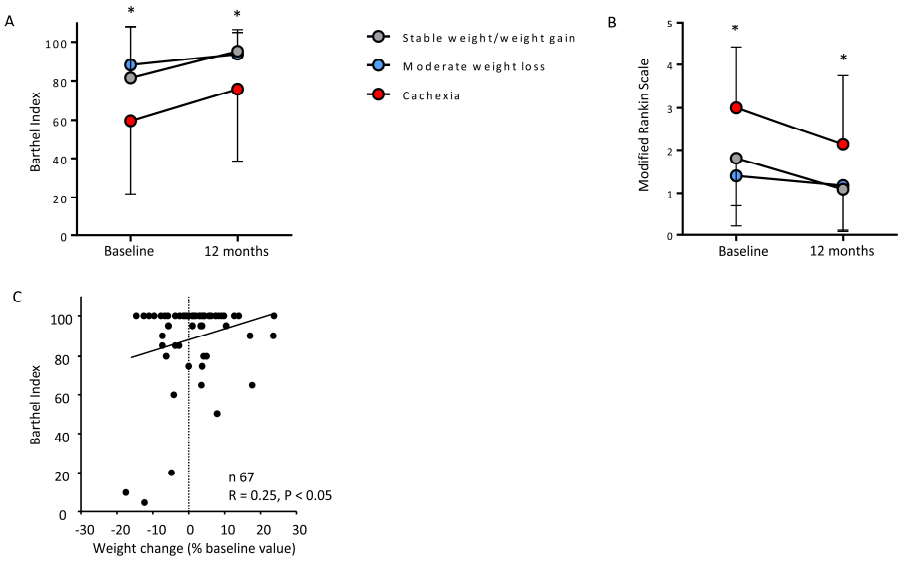
NIHSS, National Institute of Health Stroke Scale; VAS, visual analogue scale.

Table 3. Body composition in patient subgroups

Parameter	Weight gain/stable weight		Moderate weight loss		Cachexia	
	Baseline	12 months	Baseline	12 months	Baseline	12 months
Body mass index, kg/m^2	26.7 ± 3.5	28.2 ± 4.9***	28.7 ± 5.1	27.9 ± 4.9**	26.4 ± 4.8	24.2 ± 4.5**$^{\#\dagger\dagger\dagger}$
FFMI, kg/m^2, female patient	6.4 ± 0.8	6.6 ± 0.7	6.5 ± 0.04	6.6 ± 0.1	6.1 ± 0.8	6.0 ± 1.3†
FFMI, kg/m^2, male patient	8.3 ± 0.7	8.3 ± 0.8	8.1 ± 0.7	7.9 ± 0.7	7.6 ± 0.5	7.4 ± 0.6*$^{\#}$
Lean mass, kg						
Appendicular	22.2 ± 4.9	22.4 ± 4.7	22.7 ± 3.9	22.3 ± 3.5	18.6 ± 4.5	18.0 ± 4.6*$^{\#\dagger\dagger}$
Lower limbs	16.9 ± 3.4	17.2 ± 3.3*	17.7 ± 3.5	17.7 ± 3.0	14.2 ± 3.2	13.9 ± 3.4††
Upper limbs	5.4 ± 1.6	5.3 ± 1.5	5.8 ± 1.1	5.1 ± 1.4**	4.4 ± 1.3	4.1 ± 1.3**$^{\#\dagger}$
Fat mass, kg						
Appendicular	11.9 ± 3.8	12.1 ± 3.9**	10.2 ± 3.2	9.2 ± 3.2*$^{\#}$	10.0 ± 4.1	9.1 ± 4.4**$^{\#}$
Lower limbs	9.1 ± 2.9	9.8 ± 3.4	8.7 ± 2.7	7.6 ± 2.8*†	7.8 ± 2.9	7.6 ± 3.6**
Upper limbs	2.4 ± 0.8	2.5 ± 0.8	2.4 ± 0.8	1.9 ± 0.5*	2.3 ± 1.0	2.0 ± 1.3**†

FFMI, fat-free mass index.
*$P < 0.05$.
**$P < 0.01$.
***$P < 0.001$ vs. baseline.
$^{\#}P < 0.05$.
$^{\dagger}P < 0.01$ vs. weight gain/stable weight group.
$^{\dagger\dagger}P < 0.05$.
$^{\dagger\dagger\dagger}P < 0.001$ vs. moderate weight loss group.

Figure 2 (A) Assessment of functional capacity according to the Barthel Index in study subgroups. (B) Assessment of degree of disability according to the modified Rankin Scale in study subgroups. (C) Relationship between the functional outcome and weight change at 12 months follow-up



pulmonary disease has been shown previously.[25,37] In the present study, cachectic patients showed similar signs of inflammatory activation with elevated CRP levels assessed at 12 months follow-up accompanied by lean tissue depletion, low functional capacity, and reduction of body weight. A relation between systemic inflammation and loss of muscle strength and muscle thickness in population-based clinical trials has been reported previously.[27,38] In experimental setting, administration of the inflammatory markers in rats caused muscle protein breakdown.[39] Thus, our results were in accordance with previous observations.

Our recent studies investigating cachexia in patients with chronic heart failure suggested an association of cardiac cachexia with gastrointestinal congestion, increased concentration of gut bacteria, and systemic inflammation.[37,40] Further, changes in gut microbiota after stroke were linked to increased pro-inflammatory cytokines levels.[41] Several pathways linking systemic inflammation to the brain and

Figure 3 (A) Maximal handgrip strength in study subgroups. (B) Maximal quadriceps strength in study subgroups. (C) Association of fat-free mass index with maximal handgrip strength in patients with and without cachexia at 12 months follow-up

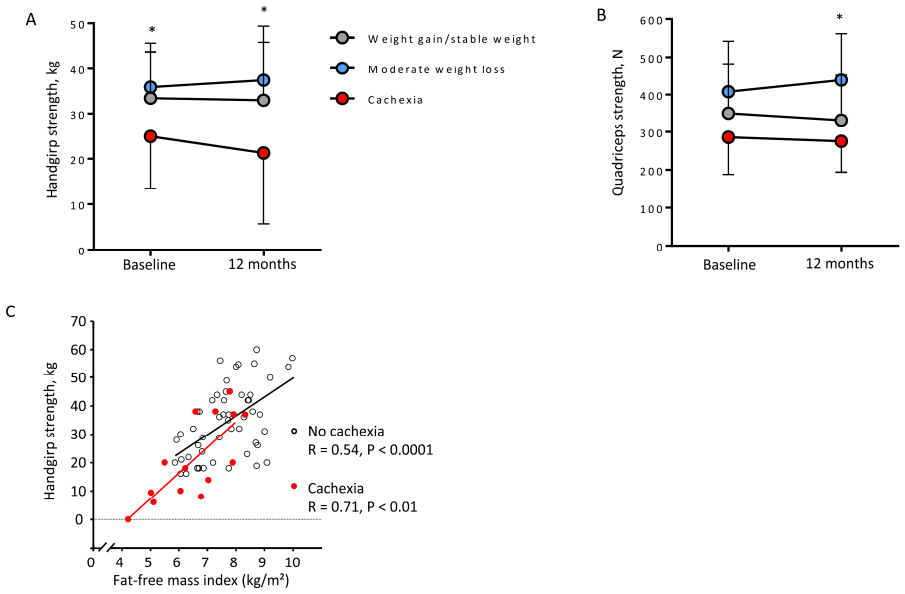


Table 4. Risk factors associated with functional dependency defined by Barthel Index <60 at 12 months follow-up

Parameter	OR	95% CI	*P*-value
Lean tissue wasting	44.8	[4.17–481.56]	0.002
Presence of cachexia	20.8	[2.09–206.15]	<0.01
Undernourished/at risk for malnutrition	14.7	[0.99–215.37]	0.05
Body mass index <25 kg/m^2	11.5	[1.19–110.67]	0.04
C-reactive protein, log[mg/L]	10.1	[1.39–73.54]	0.02
NIHSS, point	1.43	[1.07–1.90]	0.02
Delta weight loss, kg	0.82	[0.68–0.99]	0.04
Body mass index, kg/m^2	0.68	[0.50–0.93]	0.02
MNA scale, point	0.57	[0.37–0.87]	0.01
Albumin, g/L	0.75	[0.60–0.94]	0.01
FFMI, kg/m^2	0.16	[0.04–0.63]	0.01
Lean mass arms, kg	0.24	[0.06–0.92]	0.04
Lean mass legs, kg	0.58	[0.38–0.89]	0.01
Appendicular lean mass, kg	0.66	[0.47–0.93]	0.02
Handgrip strength, kg	0.89	[0.81–0.99]	0.04
Multivariable logistic model adjusted for age and sex			
I. Lean tissue wasting	137.9	[2.04–9324.7]	0.02
II. FFMI, kg/m^2	0.11	[0.13–0.99]	<0.05

FFMI, fat-free mass index; NIHSS, National Institute of Health Stroke Scale; MNA, Mini Nutritional Assessment.

responsible for development of 'sickness behaviour' with attenuated parasympathetic tone, reduced appetite, altered thermoregulation, and impaired energy metabolism were previously described.[42] Accordingly, we observed an association between systemic inflammation and reduced nutritional status in patients with stroke. Cachectic patients had the lowest appetite leading to decreased food intake. An involvement of anorexia in regulation of body composition in chronic inflammatory disease and cachexia development was suggested.[25] Therefore, ongoing systemic inflammation in chronic stroke might lead to increased metabolic drive, appetite loss, and energetic deficit resulting in proteolytic breakdown and tissue wasting.[25,43]

Functional limitations

In the present study, we showed implications of cachexia on functional outcome after stroke. Cachectic patients had the

Figure 4 (A) Self-reported appetite score according to visual analogue scale in study subgroups. (B) Nutritional status according to Mini Nutritional Assessment score in patient subgroups at 12 months follow-up. (C) Association of body weight change with score by visual analogue scale at 12 months follow-up

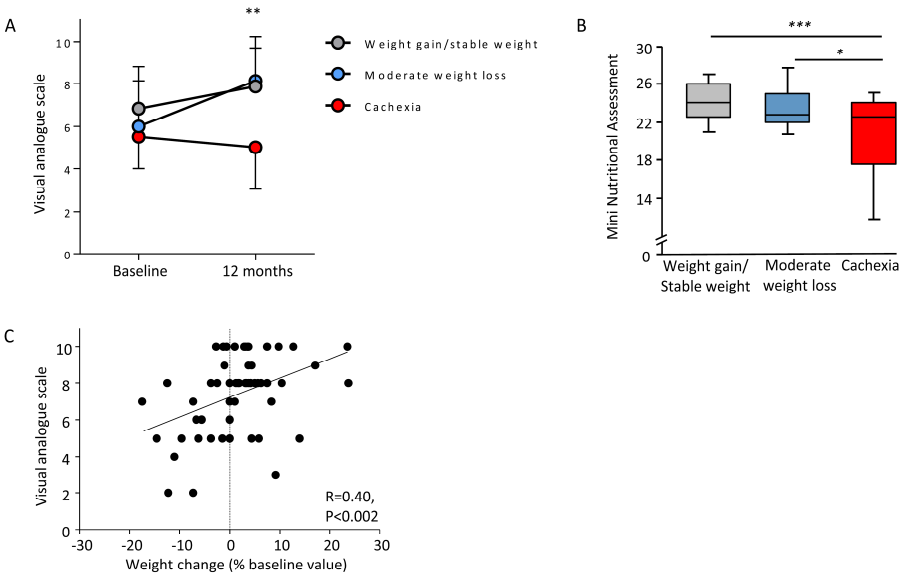


Table 5. Risk factors associated with the presence of systemic inflammation at 12 months follow-up serving as dependent variable

Parameter	OR	95% CI	*P*-value
Lean tissue wasting	5.20	[0.99–27.09]	0.05
Changes of body weight, kg	0.89	[0.80–1.01]	0.06
Appetite according to VAS, point	0.71	[0.52–0.97]	0.03
Undernourished/at risk for malnutrition	0.81	[0.69–0.99]	0.04
Modified Rankin Scale, point	1.96	[1.16–3.31]	0.01
Barthel Index, 10 points	0.68	[0.49–0.95]	0.02
Handgrip strength, kg	0.94	[0.89–0.99]	0.02

VAS, visual analogue scale.

most severe stroke-related disability across the study groups as assessed by the BI and mRS, although they significantly improved their functional status at 12 months follow-up. We showed that the presence of cachexia and the lean tissue depletion were associated with the low functional capacity as defined by the BI.[23] Further, both lower BMI and higher body weight loss were more frequently observed in patients with higher degree of functional dependence. Therefore, our findings are in accordance with the previous clinical trials, investigating cachexia in chronic diseases and suggesting its unfavourable impact on activities of daily living, clinical and functional outcome.[25,37]

Additionally, to the BI and mRS, the study protocol considered a performance of the short physical performance battery (SPPB).[22] SPPB is widely used in geriatric medicine and includes examination of standing ability, time walking of 3 or 4 m, and time to rise from the chair.[44] It became apparent in the study that the SPPB was less suitable to evaluate the functional capacity due to coordination deficit if patient had a paretic limb. Hence, merely 51% of all patients (i.e. 21% of the cachectic group) at baseline and 82% of the patients (57% of the cachectic group) at 12 months follow-up were able to complete the SPPB, which indicates a relevant floor effect as discussed previously.[12] We performed a 4 m of gait test as a part of the SPPB during the baseline and 12 months follow-up. The gait speed at baseline was 1.1 ± 0.3 vs. 0.9 ± 0.2 vs. 0.8 ± 0.4 m/s, P = 0.3 in the stable weight vs. moderate weight loss vs. cachectic subgroup, respectively. Twelve months after stroke, gait speed remained identical in all three groups due to the high frequency of paresis in these patients. Thus, due to the relevant floor effect of the test battery in the setting of stroke as well as limited insight into the functional capacity of the patients, we decided to omit these data.

Weight gain

The majority of patients in the present study increased the weight and improved their functional capacity during the first year after stroke. We observed a correlation between increasing weight and better functional outcome with higher BI, indicating a positive effect of 'obesity paradox'.[6]

Limitations

Our study has several limitations. First, the number of patients with stroke is limited. Second, only study patients with mild to moderate stroke deficit were included, thus our results are not generalizable to patients with severe stroke. Therefore, further longitudinal studies are warranted to confirm and extend our findings.

Conclusions

The observed incidence of cachexia was 21% among the patients with stroke at 12 months follow-up. Overall, more fragile patients defined by higher age, advanced neurological deficit, and functional disability were at risk for cachexia. At 12 months follow-up, cachectic patients remained with the lowest functional and physical status. Development of cachexia after stroke should be recognized as a relevant complication. Better understanding of the interaction between stroke-related brain injury and systemic metabolism seems to be required for better prevention of cachexia in patients with stroke.

Acknowledgements

The authors certify that they comply with the ethical guidelines for publishing in the Journal of Cachexia, Sarcopenia and Muscle: update 2017.[45]

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Online supplementary material

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1: Clinical characteristics of patient subgroups at 12 months follow-up

Conflict of Interest

None declared.

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2.2 Wertigkeit des C-terminalen Agrin Fragmentes als Marker des Muskelschwundes bei Patienten mit akutem Schlaganfall während der Frührehabilitation

***Scherbakov N**, Knops M, Ebner N, Valentova M, Sandek A, Grittner U, Dahinden P, Hettwer S, Schefold JC, von Haehling S, Anker SD, Joebges M, Doehner W. Evaluation of C-terminal Agrin Fragment as a marker of muscle wasting in patients after acute stroke during early rehabilitation. J Cachexia Sarcopenia Muscle. 2016; 7:60-7.*

Ein Muskelschwund in Assoziation mit einer Erkrankung wird als sekundäre Sarkopenie bezeichnet. Die Diagnose der sekundären oder krankheitsbedingten Sarkopenie bezieht sich überwiegend auf den Verlust der Muskelmasse. Dabei ist es wichtig einen robusten Biomarker für den Muskelabbau zu etablieren. In der folgenden Arbeit wurde die Wertigkeit des CAF bei den Patienten mit Schlaganfall untersucht. CAF wurde als ein neuer Biomarker für die Diagnose der Sarkopenie bei Patienten mit altersassoziierter Sarkopenie vorgeschlagen. Agrin ist ein 225 kDa schweres Protein, es wird von den präsynaptischen Neuronen in den synaptischen Spalt sezerniert und wird als Schlüsselorganisator der ACh-Rezeptoren in der postsynaptischen Membran angesehen [106,107]. Agrin wird durch Neurotrypsin abgebaut und sein Fragment, CAF22, kann im Serum nachgewiesen werden. Bei Patienten mit Schlaganfall wird häufig ein Muskelschwund beobachtet, so dass das funktionelle Outcome dadurch beeinträchtigt werden kann. In dieser Studie haben wir CAF22 als Marker des Muskelabbaus bei Schlaganfallpatienten evaluiert.

Wir untersuchten 123 Patienten (Alter 70±11 J, BMI 27,0±4,9 kg/m²) mit ischämischen oder hämorrhagischen Schlaganfall während der stationären Frührehabilitation. Die Studienuntersuchungen wurden bei Baseline, BL (23±17 Tage nach Schlaganfall) und bei Entlassung, Follow-up, FU, (49±18 Tage nach Schlaganfall) durchgeführt. Der funktionelle Status wurde anhand der BI Score und RMA Score erhoben. Muskelkraft wurde als Handgriffstärke evaluiert. Körpergewebezusammensetzung wurde mittels BIA erfasst. Zum Vergleich wurden 23 gesunde Probanden ähnlichen Alters und BMIs untersucht.

Die Patienten zeigten einen erhöhten CAF22 Serumspiegel bei BL (134,3±52,3 pM), der sich nicht komplett bei der FU (118,2±42,7 pM) im Vergleich zu gesunden Kontrollen (95, 7±31,8 pM, $p<0.001$) normalisierte. In der einfachen Regression korrelierte höherer CAF22 Serumspiegel mit niedrigeren Parametern des funktionellen Status, Handgriffstärke und Phasenwinkel als Parameter der Zellintegrität. Die verbesserte Handgriffstärke des paretischen Arms korrelierte mit dem sinkenden

CAF22 Serumspiegel bei den Patienten, die während der Frührehabilitation ihre Magermasse verbessert haben.

Diese Studie zeigte die dynamischen Profile von CAF22 Serumspiegel bei Patienten mit Schlaganfall während der stationären Frührehabilitation. Die Rolle vom CAF22 als Biomarker für den Muskelabbau soll in weiteren Studien evaluiert werden.

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Evaluation of C-terminal Agrin Fragment as a marker of muscle wasting in patients after acute stroke during early rehabilitation

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Abstract

Background C-terminal Agrin Fragment (CAF) has been proposed as a novel biomarker for sarcopenia originating from the degeneration of the neuromuscular junctions. In patients with stroke muscle wasting is a common observation that predicts functional outcome. We aimed to evaluate agrin sub-fragment CAF22 as a marker of decreased muscle mass and physical performance in the early phase after acute stroke.

Methods Patients with acute ischaemic or haemorrhagic stroke (n = 123, mean age 70 ± 11 y, body mass index BMI 27.0 ± 4.9 kg/m^2) admitted to inpatient rehabilitation were studied in comparison to 26 healthy controls of similar age and BMI. Functional assessments were performed at begin (23 ± 17 days post stroke) and at the end of the structured rehabilitation programme (49 ± 18 days post stroke) that included physical assessment, maximum hand grip strength, Rivermead motor assessment, and Barthel index. Body composition was assessed by bioelectrical impedance analysis (BIA). Serum levels of CAF22 were measured by ELISA.

Results CAF22 levels were elevated in stroke patients at admission (134.3 ± 52.3 pM) and showed incomplete recovery until discharge (118.2 ± 42.7 pM) compared to healthy controls (95.7 ± 31.8 pM, $p < 0.001$). Simple regression analyses revealed an association between CAF22 levels and parameters of physical performance, hand grip strength, and phase angle, a BIA derived measure of the muscle cellular integrity. Improvement of the handgrip strength of the paretic arm during rehabilitation was independently related to the recovery of CAF22 serum levels only in those patients who showed increased lean mass during the rehabilitation.

Conclusions CAF22 serum profiles showed a dynamic elevation and recovery in the subacute phase after acute stroke. Further studies are needed to explore the potential of CAF22 as a serum marker to monitor the muscle status in patients after stroke.

Keywords Stroke; Muscle wasting; Post-stroke rehabilitation; C-terminal Agrin Fragment; Physical performance; Skeletal muscle mass

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Introduction

Skeletal muscle wasting has been frequently observed after stroke.[1] Already within 4 h after cerebral damage an initial reduction of motoneurons in the musculature of paretic limb is observed[2] that persists in the chronic phase after stroke.[3] Loss of muscle innervation leads to muscular weakness, inactivity, and immobilization and results in muscle atrophy.

Within the first week after stroke muscle weakness occurs also in the non-paretic limb.[4] Decline of muscle mass has been observed in stroke patients within first three weeks after hemiparetic stroke.[5] Further, patients who are not able to relearn walking within 2 months after stroke revealed similar lean mass reduction in paretic and non-paretic leg.[6] A combination of mechanisms, including immobilization, disuse, inflammation, metabolic, and neurovegetative imbalance after stroke, results frequently in muscle wasting and may progress to the stroke-related sarcopenia.[1,7] The presence of stroke-specific sarcopenia has been proposed from experimental[8] and clinical data.[9,10]

Progressive degradation of muscle mass was termed as 'sarcopenia' and was originally observed in relationship to aging.[11] The prevalence of sarcopenia is about 5 to 10% in persons over 65 years of age.[12] Numerous factors such as malnutrition,[13] immobilization and disuse,[14] hormonal imbalance etc. are discussed in the multifactorial aetiology of sarcopenia.[15–18] In aging loss of motoneurons has been proposed as pathogenic and contributing to the developing of sarcopenia.[19,20]

Recently, C-terminal Agrin Fragment (CAF) has been proposed as a potential marker for sarcopenia caused by degeneration of the neuromuscular junctions (NMJs) in elderly.[21] Agrin is a heparin sulphate proteoglycan with a molecular weight of 225 kDa, which is considered as a key organizer of postsynaptic differentiation at NMJs.[22–24] Proper clustering of acetylcholine receptors (AChR) at post-synaptic basal lamina depends on agrin-mediated signalling.[22,25] Proteolytic cleavage of agrin by neuronal protease neurotrypsin at NMJs triggers inactivation and destabilization of the NMJ with subsequent muscle degradation. A sarcopenic phenotype has been observed in transgenic mouse with neurotrypsin overexpression.[26] In human plasma two stable and bio-inactive circulating fragments of agrin—AgrinC110 (cleavage at α-site) and CAF22 (cleavage at β-site) were identified *(Figure* 1).[21] It has been shown that elevated CAF22 plasma levels may indicate muscle wasting in pre-frail community-dwelling older adults because of degeneration of the NMJ.[27] The reduction of CAF22 levels after 12 week power training supports CAF22 as a marker of muscle wasting and the development of sarcopenia. In contrast, a study evaluating an effect of resistance training in older adults revealed elevation of CAF levels following 6-weeks of training.[28]

The aim of the present study was to evaluate agrin as a marker of muscle wasting in patients with stroke. Because physical exercise is an effective therapy to prevent muscle wasting,[29] we investigated a cohort of stroke patients in the early post stroke rehabilitation. We hypothesized that CAF22 might be a marker of muscle status and function during recovery after paretic stroke. We evaluated CAF22 in relation to changes in muscle mass and functional recovery during early rehabilitation period.

Patients and methods

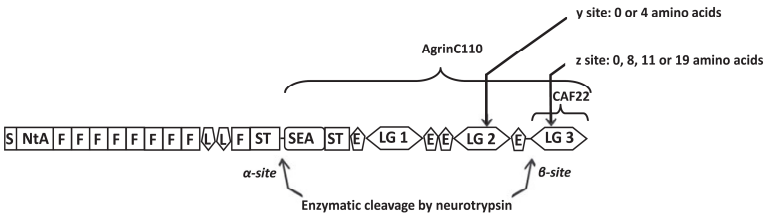
Study population and enrolment criteria

We studied 123 patients (age ranging from 42 to 98 years) with confirmed diagnosis of ischaemic or haemorrhagic stroke. Patients were admitted from October 2011 to August 2013 to neurological rehabilitation centre Brandenburgklinik Bernau, Germany. Clinical and functional examinations were performed at admission and at discharge. Within the early post-stroke hospitalized rehabilitation programme all patients were on standard medical therapy according to current guideline recommendations (including antiplatelet drugs, statins, angiotensin-converting enzyme inhibitors, and β-blocker). Exclusion criteria for this observational study were acute and chronic inflammatory diseases, acute heart failure or myocardial infarction, liver cirrhosis, acute and chronic renal failure and dialysis, immune suppressive therapy, and history of cancer within the last 5 years. Twenty six healthy individuals of similar body mass index (BMI) and age were enrolled used as control group. The research protocol was approved by the local ethics committee, and written informed consent was obtained from all subjects.

Assessment of functional capacity and physical examination

Functional independence was assessed using the Barthel index (BI) that addresses basic self-care and mobility aspects

Figure 1 Structure and cleavage sites of agrin.



with a score ranging from 0 to 100, where the lowest score indicates greater dependency.[30] Assessment of physical status included following testing: the Rivermead motor assessment gross function subscale (RMA) that scores a range of physical activities with increasing complexity from turning over in bed to hop on the affected leg 5 times.[31,32] Arm strength was analysed using the handgrip dynamometer (Saehan Corporation, Korea). The highest of three handgrip measurements was used for analysis.

Body composition

Body mass index (BMI) was calculated as a ratio of body weight and squared height (kg/m^2). Body composition was assessed by bioelectrical impedance analysis (BIA) (QuadScan 4000, Bodystat Limited, UK). The principle of BIA analyses is based on measurements of whole body resistance (*R*) and reactance (*Xc*) values[33] where *R* reflects conductivity through ionic solutions, and *Xc* reflects dielectric properties of plasma membrane measured as a phase-shift in current flow at 50 Hz. Phase angle of the whole body (ϕ, arc tangent expressing a relationship between Xc and R) is understood as bioimpedance measures of cell membranes of skeletal muscle and as indicator of cellular health.[34] BIA measurements were taken in supine position in standard condition as described previously.[35]

Blood samples

Venous blood samples were obtained under standardized conditions after overnight fasting and after 15 min of supine resting in a quiet and air conditioned room. Samples were centrifuged at 3500 rpm for 15 min (2000x g), aliquoted and stored at −80°C until analysis. CAF22 concentrations were measured using a commercially available enzyme-linked immunosorbent assay (ELISA) kit (NTCAF Elisa Kit; Neurotune, Schieren, Switzerland) as described previously.[36] The coefficient of variance of the test is 12.3% maximal deviation for serum and 5.6% maximal deviation for the used calibrator in a combined intra- and inter-plate comparison. For the tested samples, the deviation must have been lower than 20% in each double measurement. The accuracy of the calibrator curve was >0.98 (Rsqr), and the validated range of detection was 20 pM to 380 pM. In case of higher CFA values, the sample was diluted with PBS and remeasured until the value was within the detection range.

Statistical analysis

All variables were tested for normal distribution using the Kolmogorov–Smirnov test. All data were presented as mean values ± standard deviation or as median [interquartile range, IQR]. Paired Student t-test, unpaired Student t-test, and Mann–Whitney test were used as appropriate. Chi Square test was used to assess categorical distribution between groups. The relationship between variables was analysed by linear and multiple regression analyses. A value of $p < 0.05$ was considered statistically significant. For statistical analysis, standard statistical software packages were used (Statview 5.0, SAS Institute, Cary, NC).

Results

Clinical and functional characteristics before and after rehabilitation

Functional assessments were performed at admission (23 ± 17 days post stroke) and at discharge from the rehabilitation centre (49 ± 18 days post stroke).

Baseline characteristics of study population groups are shown in *Table* 1. Patients and healthy controls were of similar age and body mass index (BMI). Fifty-five per cent of the stroke patients revealed a 2.2% increase of the lean mass at discharge, whereas in the rest of the patients revealed a decline of the body lean mass by 2.6% (*Table* 2). Physical performance and muscle functional measures were significantly impaired after stroke compared to controls (data shown for the hand grip strength, *Figure* 2) and improved during rehabilitation as assessed by maximum hand grip strength, Barthel index, and Rivermead motor assessment (*Table* 2). Thus, patients presented better functional performance at discharge from the rehabilitation centre compared to admission.

CAF22 plasma level during rehabilitation

At admission, CAF22 serum level was significantly elevated (+26%) in stroke patients compared to controls ($p < 0.001$, unpaired t-test; *Figure* 3*A*). CAF22 level declined subsequently during rehabilitation but remained 17% above the control group at discharge ($p < 0.05$; *Figure* 3*A*). The mean change of CAF22 serum level between discharge and admission was expressed as a change of total CAF22 (*Table* 1). CAF22 serum levels were not significantly different in females compared to male patients (*Table* 1). However, compared to healthy controls female stroke patients showed 21% higher CAF22 level at admission (*Figure* 3*B*), whereas between male patients and controls this difference was 56% (*Figure* 3*C*). At discharge, CAF22 was 12% higher in female but still 41% higher in male patients compared to controls of the same gender. Thus, CAF22 level rise after stroke seems to be more pronounced in male than in female patients.

Table 1 Clinical characteristics of study groups

Parameters	Controls n = 26	Patients at admission n = 123	Patients at discharge n = 123
Age, y	67 ± 8	70 ± 11	70 ± 11
Gender, f/m [m, %]	17/9 [41]	49/74 [60]*	
Stroke ischaemic, n [%] / haemorrhagic, n [%]		106 [86] / 17 [16]	
Days after stroke		23 ± 17	49 ± 18$^{\#\#\#}$
CAF22, pMol	95.7 ± 31.8	134.3 ± 52.3***	118.2 ± 42.7*$^{\#\#\#}$
CAF22, pMol, female	102.6 ± 30.7	140.3 ± 51.6**	119.5 ± 35.5$^{\#\#\#}$
CAP22, pMol, male	82.7 ± 31.2	130.2 ± 52.7**	117.3 ± 47.1*$^{\#\#\#}$
Change of total CAF22, pMol			−16.1 ± 30.4
Creatinine, mg/dL	0.79 ± 0.14	0.97 ± 0.31**	0.96 ± 0.33
Sodium, mmol/L	141.5 ± 3.3	140.1 ± 4.4	140.3 ± 2.7
Potassium, mmol/L	4.4 ± 0.4	4.4 ± 0.4	4.3 ± 0.5
Body mass index, kg/m^2	25.6 ± 3.3	27.0 ± 4.9	26.0 ± 5.2
Lean mass, kg	46.9 ± 10.1	51.9 ± 11.7*	51.6 ± 11.3
Fat mass, kg	24.9 ± 6.9	25.0 ± 9.7	23.4 ± 8.8
Phase angle, ϕ	5.7 ± 1.1	5.1 ± 1.0**	5.0 ± 1.0**

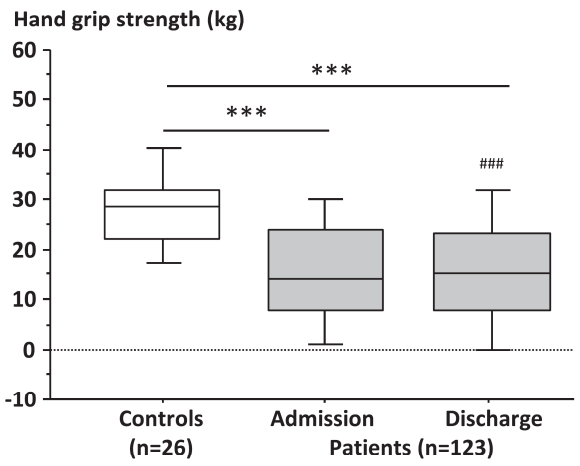
*$p < 0.05$,
**$p < 0.01$,
***$p < 0.001$ vs. controls;
$^{\#\#\#}p < 0.001$ vs. admission

Table 2 Parameters of body composition and physical performance at admission and at discharge from the rehabilitation centre

Parameters	At admission (n = 120)	At discharge (n = 120)
Lean mass increase, kg, n = 67	50.6 ± 11.8	51.7 ± 11.7***
Lean mass decrease, kg, n = 56	53.2 ± 11.7	51.7 ± 11.4***
Max hand grip strength paretic arm, kg	15.8 ± 11.6	16.0 ± 11.7***
Max hand grip strength nonparetic arm, kg	28.2 ± 11.1	29.6 ± 11.7***
Barthel Index score	60 ± 22	73 ± 20***
Rivermead Motor Assessment score	5.3 ± 2.0	7.2 ± 2.2***

***$p < 0.001$ vs. admission

Figure 2 Hand grip strength of stroke patients compared to healthy controls (***$p < 0.001$ vs. controls; $^{\#\#\#}p < 0.001$ vs. admission).



CAF22 and functional performance

In the linear regression analyses CAF22 levels were associated with BI ($r = 0.2$, $p < 0.022$), RMA score ($r = 0.2$, $p < 0.05$), hand grip strength of the non-paretic arm ($r = 0.2$, $p < 0.05$), age ($r = 0.4$, $p < 0.001$), and creatinine levels ($r = 0.7$, $p < 0.001$).

In multivariable regression analyses change of CAF22 serum level was independently associated with improvement of the hand grip strength of the paretic arm, but not in the non-paretic arm in patients who showed increased muscle mass during rehabilitation (*Table* 3*B*). However, this association was not observed in the whole study cohort (*Table* 3*A*).

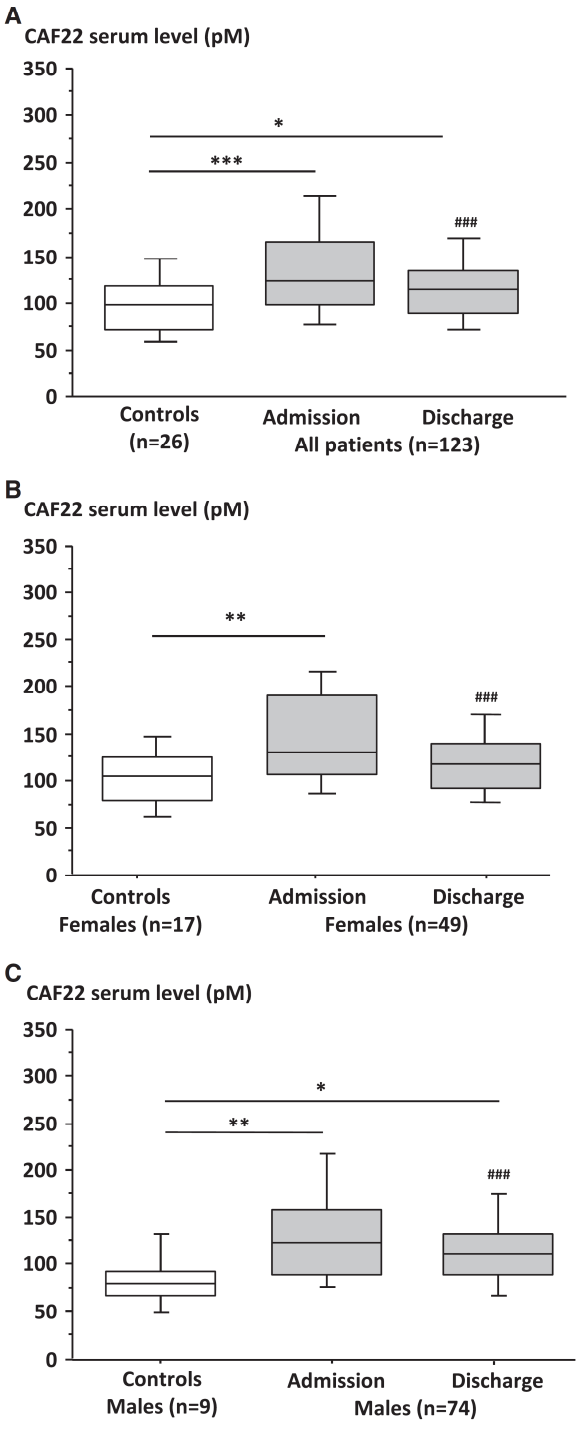
CAF22 levels and phase angle

A strong association between CAF22 level at admission and phase angle ($r = -0.351$, $p < 0.001$) was observed in simple regression analysis. After adjustment for age, creatinine level, and gender this association remained independently significant (*Table* 4).

Discussion

The major finding of the study is the elevation and dynamic change of CAF22 serum levels in patients after acute stroke. CAF22 serum levels were significantly increased in the subacute phase after stroke. During rehabilitation, an incomplete return of elevated CAF22 levels was observed. CAF22 was associated with parameters of physical and functional performance and with bioelectrical impedance phase angle. Further, an improvement of hand grip strength of the paretic

Figure 3 CAF22 plasma level in stroke-patients at admission to rehabilitation centre and at discharge compared to controls: All patients (A); Female patients (B); Male patients (C) (***$p < 0.001$, **$p < 0.01$, *$p < 0.05$ vs. controls; ###$p < 0.001$ vs. admission).



arm during rehabilitation was independently associated with the reduction of CAF22 serum levels in patients who showed an increase of muscle mass during rehabilitation.

We observed elevated CAF22 serum levels at admission to inpatient rehabilitation. CAF22 levels decreased during 4 weeks of a rehabilitation programme but were still higher at discharge compared to healthy subjects. Our findings are in line with previous reports showing a reduction of elevated CAF22 levels after a training programme in a cohort of elder subjects.[27] These authors suggested CAF22 as a potential marker of age-associated sarcopenia caused by the degeneration of the NMJ. In our study patients were admitted to the rehabilitation hospital 3 weeks after stroke. At this time point patients revealed significantly reduced handgrip strength in parallel to elevated CAF22 serum levels. In addition, our analyses have shown an independent association between reduction of CAF22 serum levels and improvement of hand grip strength of the paretic arm in patients with increased muscle mass during rehabilitation. Decreasing of CAF22 levels after 4 weeks of a physical rehabilitation programme might therefore suggest termination of the muscle wasting and reactive NMJs recovery.

Recently, CAF22 has been evaluated as a biomarker of kidney function. Indeed, agrin is expressed in the kidney and CAF22 has been related to the damage of the glomerular basement membrane.[37,38] In our study patients with renal failure as well as with dialysis were excluded. We observed a strong correlation between CAF22 and creatinine, although the reduction of the creatinine serum level at discharge was not significant in contrast to the significant reduction of the CAF22 serum levels. Thus, it is not clear to which extent CAF22 serum levels reflect the kidney function in stroke patients. Yet, a confounder for CAF22 serum levels because of kidney function could not be excluded and may be seen as a limitation of the study.

In addition, the existence of several splicing isoforms of agrin should be considered in the evaluation of CAF22 as a biomarker for sarcopenia.[22,39] Agrin function is highly regulated by alternative splicing and proteolytic processing. Splicing isoforms containing 0 or 4 amino acid inserts at the y splicing site of the LG2 domain and 0, 8, 11, or 19 (8 + 11) amino acid inserts at the z splicing site of the LG3 domain of the C-terminus have been investigated (*Figure* 1).[23,40] The neural agrin containing 4 and 8 amino acid inserts at the y and z sites, respectively, has a high affinity to the AChR clustering, while muscle agrin and agrin found in other non-neuronal cells lacks inserts and fails to cluster AChRs.[41] However, splicing isoforms of agrin lacking inserts have been found in NMJs (motor neurons, skeletal muscle, and Schwann cells), in the central nervous system and peripheral tissues (lung and kidney).[23] The ELISA assay used in the present study predominately identifies the z0 splicing isoform. Previous experiments have shown that the z0 splicing isoform is at least 10–20 folds overrepresented over the insert baring

Table 3 A). Multiple regression analyses investigating change of hand grip strength during rehabilitation in stroke patients (n = 123)

Parameter	Coefficient	p	r
1. Change of hand grip strength of paretic arm vs.			0.286
Gender	0.059	0.579	
Age	−0.229	0.035	
Change of CAF22	−0.175	0.097	
Creatinine	−0.102	0.353	
2. Change of hand grip strength of nonparetic arm vs.			0.294
Gender	0.141	0.151	
Age	−0.157	0.120	
Change of CAF22	−0.121	0.223	
Creatinine	−0.189	0.069	

Table 3 B.) Multiple regression analyses investigating changes in hand grip strength at discharge and admission in stroke patients with improved lean mass during rehabilitation (n = 67)

Parameter	Coefficient	p	r
1. Change of hand grip strength of paretic arm vs.			0.318
Gender	0.045	0.749	
Age	−0.218	0.134	
Change of CAF22	−0.292	0.045	
Creatinine	−0.089	0.563	
2. Change of hand grip strength of nonparetic arm vs.			0.301
Gender	0.046	0.723	
Age	−0.100	0.465	
Change of CAF22	−0.180	0.211	
Creatinine	−0.293	0.055	

Table 4 Multiple regression analysis investigating phase angle as a parameter of cell membrane integrity in stroke patients

Parameter	Coefficient	p	r
Phase angle vs.			0.523
Gender	0.170	0.055	
Age	−0.341	0.0003	
Creatinine	0.095	0.422	
CAF22	−0.267	0.026	

splice isoforms (Western blots and internal analyses). The appearance of the z0 splicing variant of the C-terminal agrin fragments in blood, however, represents the activity of neurotrypsin.[42] Further, a vast amount of z0 isoform of agrin is present on the postsynaptic side, which is also cleavable by neurotrypsin. Muscle agrin is concentrated at the nerve-induced AChR clusters where it contributes to maturation and stabilization of the receptors.[43,44] Therefore, the postsynaptic muscle agrin is able to liberate CAF22, which may then be secreted and may appear in the blood stream. Thus, we believe that in stroke patients a significant amount of the CAF22 in serum origins from the nervous tissue or postsynaptic tissue because of denervation and degradation of the NMJs. However, optimization of the ELISA assay towards identifying of the neuronal agrin might improve the specificity and sensitivity of the results and may contribute to the establishing of CAF22 as a marker of muscle wasting caused by NMJ degeneration.

Our analyses revealed an independent association of the BIA phase angle with CAF22 levels. Phase angle has been shown in relation to the muscle mass and muscle strength; therefore phase angle represents a simple index of the integrity of the skeletal muscle cell membranes.[34] A previous study in patients with neuromuscular diseases has shown a decline of phase angle in parallel with disease progression that was accompanied by a subsequent decline of muscle strength and quality of muscle tissue.[45] Therefore our data suggest lower CAF22 to indicate a better cellular integrity of muscle tissue.

The present study had same limitations. As mentioned above, renal function may be a relevant confounder of CAF 22 levels. Further, BIA assessment may provide only limited information on body composition and more detailed information on tissue distribution and composition may be desirable. Previous studies comparing body composition assessment by BIA and dual-energy X-ray absorptiometry DEXA, or by BIA and magnet resonance imaging MRI, confirmed reliable agreement between these methods.[46–50] Another study examining muscle mass assessed by BIA and MRI indicated a strong relation between muscle mass and body resistance.[49] However, underestimation of the fat mass and over predicting of the fat-free mass assessed by BIA has been reported.[47] In addition, the presence of oedema may influence BIA measurements. The effect of the whole body water changes and its dependence from the sodium plasma concentrations has been discussed previously.[51] However, in the

present study patients were free of peripheral oedema and sodium plasma levels remained unchanged suggesting stable fluid balance during the observation period.

In conclusion, CAF22 serum levels were elevated in the subacute phase after acute stroke and fell during rehabilitation. Associations between CAF22 and parameters of physical performance, muscle strength, and muscle membrane integrity have been observed. In multivariable analysis recovery of increased CAF22 levels was independently associated with improved hand grip strength only in those patients who showed increasing lean tissue during rehabilitation but not in the entire cohort. The present data are promising to explore further the role CAF22 as a potential serum marker for monitoring muscle status in patients after stroke. Further studies are warranted including optimization of the analytic assay of CAF to evaluate the role of CAF22 as a serum marker of muscle wasting in stroke patients.

Conflict of interest

NS, MK, NE, MV, AS, UG, SvH, SDA, UD, MJ, and WD: no conflict of interest. PD and SH are employed by Neurotune AG that develops the CAF biomarker.

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2.3 Eisenmangel bei Patienten mit akutem und chronischem ischämischen Schlaganfall

***Scherbakov N**, Sandek A, Valentova M, Mayer A, von Haehling S, Jankowska E, Anker SD, Doehner W. Iron Deficiency and Reduced Muscle Strength in Patients with Acute and Chronic Ischemic Stroke. J Clin Med. 2022;11:595.*

Eisenmangel (Iron Deficiency, ID) ist eine häufige Komorbidität bei geriatrischen Patienten und Patienten mit chronischen Erkrankungen wie chronische Herzinsuffizienz, chronische Nierenerkrankung oder onkologische Erkrankungen. Patienten mit ID haben eine verminderte körperliche Belastbarkeit, eine reduzierte Lebensqualität und eine schlechtere klinische Prognose. Die Rolle von ID bei Patienten mit Schlaganfall ist nicht ausreichend untersucht. Das Ziel dieser Arbeit war: 1) die Prävalenz vom ID bei Patienten im Akutstadium und ein Jahr nach Schlaganfall zu untersuchen; 2) den Impact vom ID auf funktionellen Status und Muskelkraft zu bestimmen.

Wir haben eine Kohorte von 140 Patienten (69±13 Jahre, BMI 27,7±4,6 kg/m²) mit einem ischämischen Schlaganfall im Versorgungsgebiet der A. cerebri media (MCA) bei Baseline, BL (3±2 Tage nach Schlaganfall) untersucht. 64 Patienten (FU Kohorte) wurden zusätzlich ein Jahr nach Schlaganfall bei Follow-up, FU (382±27 Tage) untersucht. ID wurde als Serumferritin ≤100 µg/l oder 100-300 µg/l und Transferrin Sättigung (TSAT) <20% definiert. Der neurologische und funktionelle Status wurde mittels NIHSS und mRS ermittelt. Isometrische Muskelkraft wurde an unterer (M. Quadriceps) und an oberer Extremität (Handgriffstärke, HGS) gemessen.

Die Prävalenz von ID in der Gesamtkohorte lag bei 48%, in der FU Kohorte lag er bei 52% und ist auf 77% bei FU gestiegen. Neurologischer und funktioneller Status war bei Patienten mit ID und ohne ID ähnlich. Bei BL war die Muskelkraft bei Patienten mit ID im Vergleich zu Patienten ohne ID reduziert (M. Quadriceps: 332±130 N vs. 391±143 N, P=0.06; HGS: 33,8±13,2 kg vs. 26,5±10,4 kg, P<0,001). Ein Jahr nach Schlaganfall verbesserte sich die Muskelkraft lediglich bei Patienten, bei denen sich der Eisenmangel normalisiert hatte (ΔHGS: 4,6±8,3 kg vs. -0.7±6,5 kg, P<0.05). Patienten mit ID verblieben mit reduzierter Muskelkraft (HGS: 28,2±12,5 vs. 44,0±8,6 kg, p<0.0001). Diese Studie zeigt eine höhere Prävalenz von ID bei Patienten mit Schlaganfall, die nach einem Jahr sogar weiter steigt. Die Patienten mit ID haben eine geringere Muskelkraft gegenüber den Patienten ohne ID. Die Muskelkraft verbesserte sich nicht bei Patienten mit ID ein Jahr nach dem Schlaganfall.

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Iron Deficiency and Reduced Muscle Strength in Patients with Acute and Chronic Ischemic Stroke

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Abstract: (1) Introduction: Iron deficiency (ID) contributes to impaired functional performance and reduced quality of life in patients with chronic illnesses. The role of ID in stroke is unclear. The aim of this prospective study was to evaluate the prevalence of ID and to evaluate its association with long-term functional outcome in patients with ischemic stroke. (2) Patients and Methods: 140 patients (age 69 ± 13 years, BMI 27.7 ± 4.6 kg/m^2, mean ± SD) admitted to a university hospital stroke Unit, with acute ischemic stroke of the middle cerebral artery were consecutively recruited to this observational study. Study examinations were completed after admission (3 ± 2 days after acute stroke) and at one-year follow up (N = 64, 382 ± 27 days after stroke). Neurological status was evaluated according to the National Institute of Health Stroke Scale (NIHSS) and the modified Rankin scale (mRS). Muscle isometric strength of the non-affected limb was assessed by the maximum handgrip test and knee extension leg test. ID was diagnosed with serum ferritin levels ≤ 100 µg/L (ID Type I) or 100–300 µg/L if transferrin saturation (TSAT) < 20% (ID Type II). (3) Results: The prevalence of ID in acute stroke patients was 48% (N = 67), with about two-thirds of patients (N = 45) displaying ID Type I and one-third (N = 22) Type II. Handgrip strength (HGS) and quadriceps muscle strength were reduced in patients with ID compared to patients without ID at baseline (HGS: 26.5 ± 10.4 vs. 33.8 ± 13.2 kg, p < 0.001 and quadriceps: 332 ± 130 vs. 391 ± 143 N, p = 0.06). One year after stroke, prevalence of ID increased to 77% (p = 0.001). While an improvement of HGS was observed in patients with normal iron status, patients with ID had no improvement in HGS difference (4.6 ± 8.3 vs. −0.7 ± 6.5 kg, p < 0.05). Patients with ID remained with lower HGS compared to patients with normal iron status (28.2 ± 12.5 vs. 44.0 ± 8.6 kg, p < 0.0001). (4) Conclusions: Prevalence of ID was high in patients after acute stroke and further increased one year after stroke. ID was associated with lower muscle strength in acute stroke patients. In patients with ID, skeletal muscle strength did not improve one year after stroke.

Keywords: iron deficiency; prevalence; acute ischemic stroke; chronic stroke; muscle strength; functional outcome

1. Introduction

Stroke is one of the leading causes of disability in adult life with a global annual incidence rate over 12 million cases [1]. Clinical outcome after stroke depends among other factors on the presence of comorbidities, such as hypertension, diabetes mellitus, heart failure (HF), or chronic kidney disease (CKD) [2–4]. Growing evidence suggests a considerable impact of iron deficiency (ID) on clinical course, prognosis, and quality of life in geriatric patients, as well as in patients with chronic diseases, such as chronic HF, cancer, and CKD [5–8].

A well-balanced iron metabolism plays a central role in the maintenance of numerous biological processes, including erythropoiesis, oxidative metabolism, immune response, and neurotransmission [9]. Physiologically, the body absorbs 7–10% of dietary iron per day, which suggests that malnutrition and/or malabsorption may have a major impact on iron balance [10]. In chronic inflammatory conditions, sufficient absorption of iron by the gastrointestinal tract and cellular iron export from the body iron stores is inhibited, leading to development of functional ID [11,12]. Inadequate nutritional iron uptake or absorption, as well as excessive blood loss, are the main causes leading to the development of absolute ID [13]. Biochemically, ID is manifested when the extracellular iron of the bone marrow, ferritin plasma levels, and transferrin saturation are low [13].

Up to date, a presence of ID, ID type, and its impact on clinical outcome remained not sufficiently studied in stroke. We hypothesized that ID is associated with low functional performance in patients with stroke. In this observational study, we aimed to evaluate the prevalence of ID in patients with acute stroke and at one year after stroke. Additionally, functional outcome in relation to ID after acute stroke and at one year after the event was investigated.

2. Methods

2.1. Study Design and Population

We prospectively studied 140 patients with acute ischemic stroke (AIS) in the territory of the middle cerebral artery (MCA), participating in the longitudinal prospective observational Body Size in Stroke Study [14] (BoSSS, German registry for clinical trials number DRKS00000514). The patients with mild to moderate neurological deficit (defined by the National Institute of Health Stroke Scale (NIHSS) as $\leq$12 points) were consecutively enrolled within 48 h after stroke onset, being admitted to the Stroke Unit at a tertiary university center (Charité University Hospital Berlin, Campus Virchow Clinic, Berlin, Germany).

Stroke was classified according to Trial of ORG 10172 in Acute Stroke Treatment (TOAST) classification, etiology of cardio embolism, large-artery atherosclerosis, small-vessel occlusion, and stroke of undetermined etiology [15]. One year after stroke, patients were invited to a follow up examination (Follow up cohort, FU cohort).

The study was approved by the Ethics Committee of Charité University Hospital Berlin (EA2/008/09), and all patients gave written informed consent.

2.2. Assessment of Functional Status

Study examinations were performed at baseline (3 $\pm$ 2 days after acute stroke) and at one-year follow up (FU, mean 382 $\pm$ 27 days after stroke). Functional status was assessed by the modified Rankin Scale (mRS), which measures physical independency by assessment of the body function, activity, and participation in daily tasks on the scale ranging from "0" (no symptoms) to "6" (death) [16].

Short physical performance battery (SPPB) was performed to assess functional capacity. SPPB includes examinations of standing ability with both feet together in the side-by-side, semi-tandem, and tandem positions; 4-m walk; and time taken to rise five times from the chair and return to the seated position. The score ranges from 0 (not attended) to 12 points (completed) [17].

Isometric muscle strength of the hand was assessed by the handgrip strength (HGS) test using a handgrip dynamometer (Saehan Corporation, Changwon, Korea). The highest

of three handgrip measurements of the non-paretic or strongest arm was used for analysis. HGS below mean was considered as low muscle strength (low HGS).

Maximal isometric muscle strength of the quadriceps muscle (Newton, *N*) was measured as described previously [18]. Briefly, the freely hanging legs of the sitting patients were connected at the ankle with a pressure transducer (Multitrace 2, Lectromed, Jersey, Channel Islands), and maximal isometric strength was assessed from the best of three contractions on each leg, with a resting period of at least 60 s in between.

2.3. Body Composition and Nutritional Status

Appetite (the subjective desire to eat) was assessed according to the visual analogue scale (VAS) ranging from "0" (no appetite at all) to "10" (always a very good appetite) [19]. None of the patients included in our study had dysphagia on a clinically relevant level (preventing oral feeding) and none were fed enterally or parenterally. The nutritional status was assessed by Mini Nutritional Assessment (MNA) at 12 months as follows: normal nutritional status was considered if the patients achieved $\geq$24 points, and all other patients were considered to have low nutritional status [20].

The body mass index (BMI) was calculated as a ratio of body weight to height squared (kg/m^2).

2.4. Blood Sampling and Iron Deficiency

Venous blood samples we obtained in all patients after 12 h of overnight fasting. Standard biochemical parameters were assessed by routine laboratory measurement. Normal iron status was defined by a serum ferritin > 100 µg/mL and transferrin saturation (TSAT) $\geq$ 20% [21]. Iron deficiency type I (ID I) was considered when plasma ferritin levels were $\leq$100 µg/mL, and iron deficiency type II (ID II) was considered for plasma ferritin levels of 100–300 µg/L and TSAT < 20% [22]. Anemia was defined by hemoglobin plasma levels of fewer than 12 g/L in females and 13 g/L in males [13]. Systemic inflammation was present if the C-reactive protein (CrP) plasma level was over 6.1 mg/dL, as defined previously [23].

2.5. Statistical Analysis

All data are presented as means $\pm$ standard deviation (SD), median [interquartile range (IQR)], or percentage as appropriate. All variables were tested for normal distribution using the Kolmogorov-Smirnov test. Serum levels of CrP were non-normally distributed, and statistical comparisons between subgroups were made using analysis of variance (ANOVA), followed by Fisher's post hoc test, Mann–Whitney or Kruskal–Wallis test, or analysis of covariance (ANCOVA). The Chi square test was used to assess categorical distribution between the groups. Multivariable models for associations of risk factors with low HGS were applied (logistic regression analysis), including all factors showing a *p*-value $\leq$ 0.1 in univariable analysis. Furthermore, age and BMI were added. Odds ratios with 95% confidence intervals (OR [95% CI]) were reported. A value of $p < 0.05$ was considered statistically significant. A total of 76 patients (54%) without data at follow up were excluded from follow-up analyses. Statistical analyses were performed with the StatView 5.0 software package (SAS Institute Inc., Cary, NC, USA).

3. Results

3.1. Baseline

Baseline clinical characteristics of all patients with acute ischemic stroke (*N* = 140) are presented in Table 1. Study examinations were performed at mean 3 $\pm$ 2 days after stroke.

Table 1. Baseline characteristics of study population.

Clinical Parameters	All Patients N = 140	Normal Iron N = 73	ID N = 67	ID Type I N = 45	ID Type II N = 22	p Value ID vs. Normal Iron	p Value ID I vs. ID II vs. Normal Iron
Age, y, mean ± SD	69 ± 13	67 ± 12	70 ± 14	66 ± 14	77 ± 12 *	n.s.	<0.01
Body mass index, kg/m^2, mean ± SD	27.7 ± 4.6	28.3 ± 4.8	27.1 ± 4.2	26.0 ± 3.8	27.5 ± 4.3	n.s.	n.s.
Systolic RR, mmHg, mean ± SD	136 ± 28	137 ± 33	135 ± 21	146 ± 18	136 ± 22	n.s.	n.s.
Diastolic RR, mmHg, mean ± SD	79 ± 14	81 ± 13	77 ± 14	84 ± 10	75 ± 16	n.s.	n.s.
Female sex N, %	55 (39)	17 (23)	38 (57)	26 (58)	12 (55)	<0.001	<0.001
Self-reported appetite	6.5 ± 2.2	6.7 ± 2.1	6.3 ±2.3	6.8 ± 2.1	5.4 ± 2.4 *	n.s.	0.05
Stroke severity National Institute of Health Stroke Scale (NIHSS)							
Mean score ± SD	4.7 ± 3.4	4.8 ± 3.6	4.6 ± 3.1	4.1 ± 2.7	5.6 ± 3.6	n.s	n.s.
0–4, N (%)	83 (59)	42 (57)	41 (62)	32 (71)	9 (41)	n.s.	n.s.
Trial of ORG 10172 in Acute Stroke Treatment							
Cardioembolic, N (%)	44 (31)	20 (27)	24 (36)	12 (27)	12 (55) *	n.s.	<0.05
Large-artery atherosclerosis, N (%)	49 (35)	26 (36)	23 (35)	16 (36)	7 (32)	n.s.	n.s.
Small-vessel occlusion, N (%)	25 (18)	14 (19)	11 (16)	9 (20)	2 (9)	n.s.	n.s.
Stroke of undetermined etiology	22 (16)	13 (18)	9 (13)	8 (17)	1 (4)	n.s.	n.s.
Physical status Modified Rankin Scale (mRS)							
Mean score ± SD	2.4 ± 1.5	2.4 ± 1.6	2.4 ± 1.6	2.1 ± 1.3	2.9 ± 1.6	n.s	n.s.
0–1, N (%)	58 (41)	32 (44)	26 (39)	19 (42)	7 (32)	n.s.	n.s.
Low Handgrip strength, N (%)	61 (44)	28 (38)	33 (49)	19 (42)	14 (64)	n.s.	n.s.
Comorbidities							
Diabetes mellitus, N (%)	40 (29)	19 (26)	21 (38)	13 (36)	7 (33)	n.s.	n.s.
Arterial hypertension, N (%)	96 (69)	49 (67)	47 (70)	31 (69)	16 (76)	n.s.	n.s.
Dyslipidemia, N (%)	45 (32)	22 (30)	23 (34)	17 (38)	6 (27)	n.s.	n.s.
Anemia, N (%)	25 (19)	7 (10)	18 (27)	9 (20)	9 (41)	<0.01	<0.01
Cardiovascular disease, N (%)	56 (40)	29 (40)	29 (43)	15 (33)	5 (23)	n.s.	n.s.
Biochemistry							
Hemoglobin, mg/dL, mean ± SD	14.0 ± 1.9	14.6 ± 1.7	13.3 ± 1.8	13.4 ± 1.8	13.1 ± 1.9	n.s.	0.0001
White blood cells count	8.3 ± 2.5	8.1 ± 1.9	8.7 ± 3.1	8.1 ± 2.3	10.1 ± 4.2 **	n.s.	<0.01
Creatinine, mg/dL, mean ± SD	1.0 ± 0.4	1.0 ± 0.4	1.0 ± 0.4	1.0 ± 0.4	0.9 ± 1.9	n.s.	n.s.
Cholesterol, mg/dL, mean ± SD	186 ± 43	189 ± 37	182 ± 49	190 ± 50	166 ± 43 *	n.s.	n.s.
High density lipoprotein, mg/dL, mean ± SD	49 ± 15	46 ± 12	51 ± 16	54 ± 17 *	46 ± 12	<0.05	<0.05
Low density lipoprotein, mg/dL, mean ± SD	110 ± 38	115 ± 34	104 ± 41	109 ± 39	93 ± 45	n.s.	n.s.
Hemoglobin A1c, %, median [IQR]	5.9 [5.4–6.5]	5.8 [5.4–6.5]	5.9 [5.5–6.5]	5.8 [5.5–6.7]	5.6 [5.6–6.6]	n.s	n.s.
C-reactive protein, mg/L, median [IQR]	4.8 [1.7–11.8]	4.1 [1.7–12]	6.6 [1.7–10.35]	4.1 [1.7–7]	16.7 [7.2–26.2] *	n.s	<0.01
Systemic inflammation, N (%)	63 (45)	30 (41)	33 (49)	16 (35)	17 (77) *	n.s.	n.s.
Medication							
Antiplatelet drugs, N (%)	120 (86)	61 (84)	59 (88)	41 (91)	18 (82)	n.s.	n.s.
Anticoagulants, N (%)	29 (21)	16 (22)	13 (19)	6 (13)	7 (32)	n.s.	n.s.
Proton pump inhibitors, N (%)	34 (24)	16 (22)	18 (27)	13 (29)	5 (23)	n.s.	n.s.
β-blocker, N (%)	57 (41)	28 (38)	29 (43)	17 (38)	12 (55)	n.s.	n.s.
ACE-inhibitors, N (%)	65 (46)	39 (53)	26 (39)	15 (45)	11 (50)	n.s.	n.s.
Ca^{2+}-channel antagonists, N (%)	14 (10)	7 (10)	7 (19)	5 (11)	2 (9)	n.s.	n.s.
Angiotensin II receptor blockers, N (%)	4 (3)	2 (3)	2 (3)	1 (2)	1 (5)	n.s.	n.s.
Diuretics, N (%)	29 (21)	12 (16)	17 (25)	10 (22)	7 (32)	n.s.	n.s.
Statins, N (%)	100 (71)	53 (73)	47 (70)	37 (82)	10 (45)	n.s.	n.s.

ACE, angiotensin converting enzyme; IQR, interquartile range; LDL, high-density lipoprotein; SD, standard deviation. * $p < 0.05$ vs. Normal Iron; ** $p < 0.01$ vs. Normal Iron. n.s., non-significant.

3.1.1. Iron Status at Baseline

Iron deficiency was present in 67 patients (48%) (Table 1, Figure 1A). ID was more frequently observed in women (57%) compared to men (43%, $p < 0.001$). There were no significant differences regarding clinical characteristics, medication, and frequency of comorbidities, except anemia (Table 1). Patients with and without ID showed a similar severity of neurologic deficit after stroke, as indicated by the NIHSS scale, and functional dependency, as indicated by the mRS.

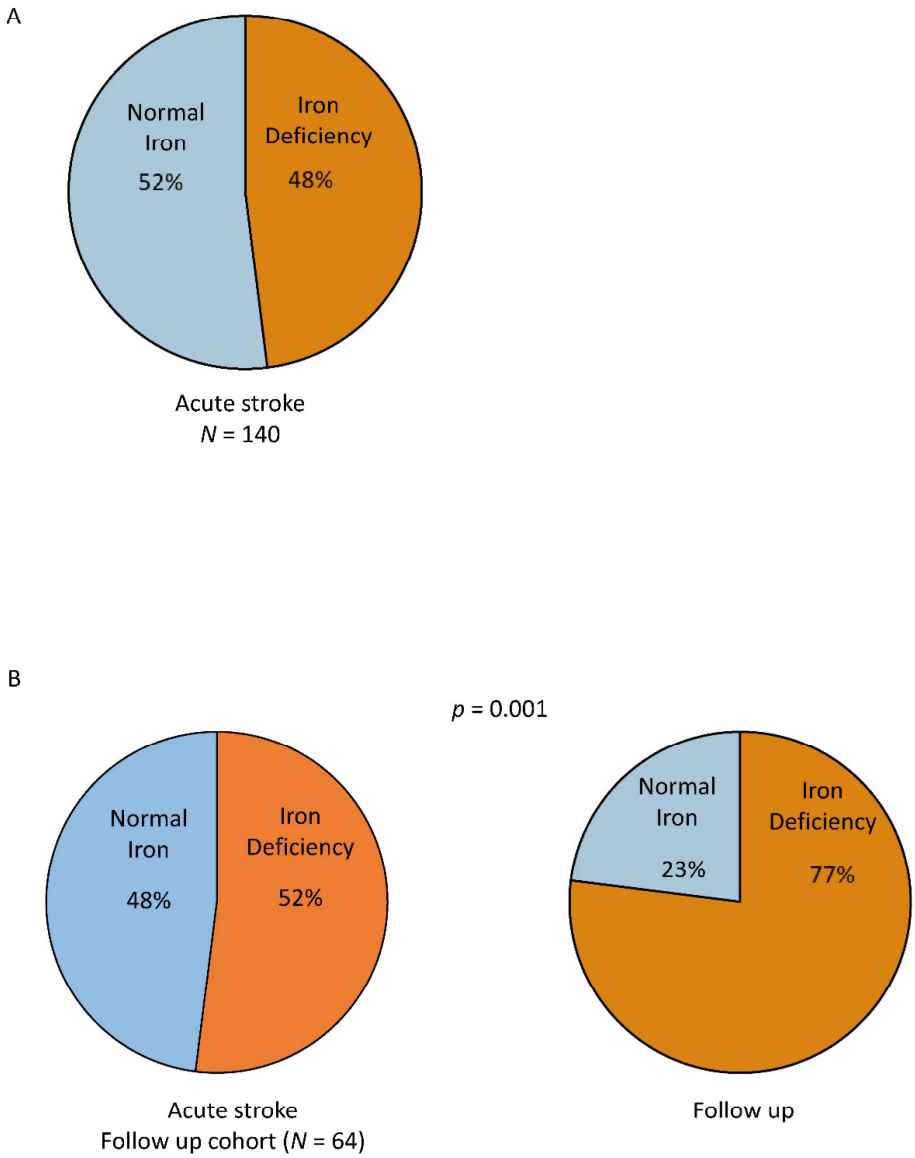

Figure 1. The prevalence of iron deficiency in acute ischemic stroke assessed at baseline (**A**) and in the follow up cohort at baseline and at one-year follow up (**B**).

ID type I was found in 32% of patients, and ID type II was found in 16% of patients. Patients with ID II were older, more frequently had a cardioembolic type of stroke, and more frequently had systemic inflammation and elevated white blood cell counts compared to patients with ID type I and patients with normal iron status (Table 1).

3.1.2. Physical Status at Baseline

At baseline, patients with ID showed lower maximal HGS compared to patients with normal iron status (mean 26.5 ± 10.4 vs. 33.8 ± 13.3 kg, $p < 0.001$). In subgroup analysis, the lower HGS was observed in patients with ID type II, followed by patients with ID type I vs. patients with Normal Iron (mean 23.0 ± 8.8 vs. 28.0 ± 10.7 vs. 33.8 ± 13.3 kg, $p < 0.01$, Figure 2).

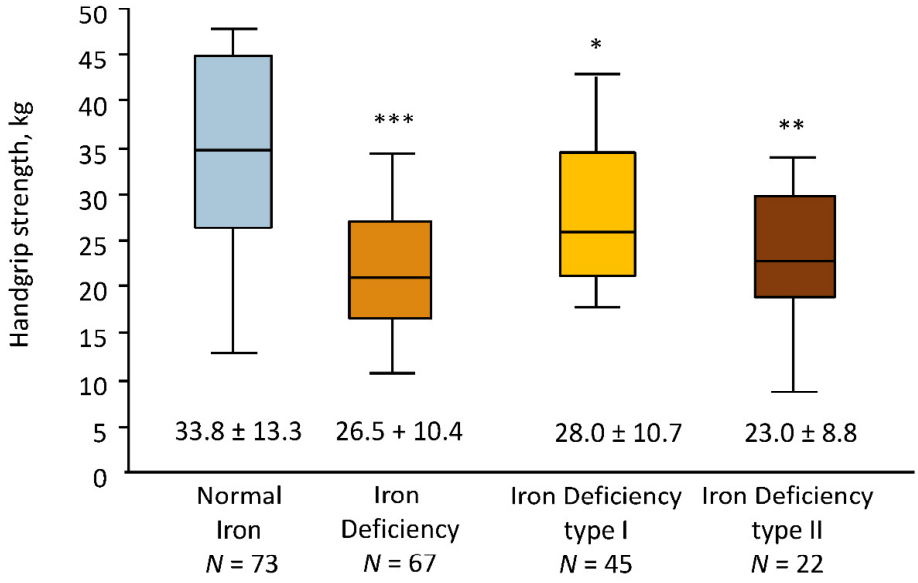

Figure 2. Handgrip strength at baseline in the study cohort divided into groups according to the presence of iron deficiency: normal iron status (normal iron), iron deficiency (ID), and categories of iron deficiency (ID type I and ID type II). * $p < 0.05$ vs. Normal Iron; ** $p < 0.01$ vs. Normal Iron; *** $p < 0.001$ vs. Normal Iron.

Of all patients, 78 patients (56%) were able to perform the quadriceps strength test. Patients with ID showed a trend towards lower quadriceps muscle strength compared to the patients with normal iron status (mean 332 ± 130 vs. 391 ± 143 *N*, $p = 0.06$) independently of their type of ID (I or II) (not shown).

SPPB was performed in 50% of patients with ID and with normal iron status. There was no significant difference either in frequency of attendance to the SPPB or in score values between both subgroups (Supplementary Materials Table S3).

3.1.3. Nutritional Status at Baseline

At baseline, there was no difference in self-reported appetite according to the visual analogue scale between the patients with ID and normal iron status. However, patients with ID type II reported the lowest appetite compared to patients with ID type I and Normal Iron (mean 5.4 ± 2.4 vs. 6.8 ± 2.1 vs. 6.7 ± 2.1, $p = 0.05$, respectively, Table 1).

3.1.4. Regression Analyses of Handgrip Strength at Baseline

Mean HGS in female patients was 21 + 9 kg and in male patients was 36 + 11 kg. Notably, those patients with ID and TSAT < 20% showed more often a lower HGS in comparison to patients with ID and TSAT ≥ 20% (64% vs. 36%, $p = 0.04$).

In univariable logistic regression, low HGS was associated with the presence of ID, ID type II, TSAT < 20%, and age in the whole patients' cohort (Table 2). Low HGS remained associated with ID type II after adjustment for BMI (Model 1). When analyzing low iron status only by marker TSAT < 20% low HGS was independently associated with low iron status after multivariable adjustment for BMI, age, and inflammation (Model 2).

Table 2. Logistic regression analyses applying presence of handgrip strength below mean as a dependent variable at baseline.

Parameter	OR	95% CI	*p*	OR	95% CI	*p*	OR	95% CI	*p*
		Univariate			**Model 1**			**Model 2**	
Transferrin saturation < 20%	3.81	1.74–8.33	<0.001				3.0	1.24–7.18	<0.05
Presence of ID	2.04	1.00–4.15	<0.05						
Presence of ID I	0.96	0.44–2.08	0.9						
Presence of ID II	4.42	1.25–15.65	0.02	4.35	1.23–15.45	0.03			
BMI (per kg/m^2 increase)	1.07	0.98–1.16	0.1	0.96	0.88–1.04	0.3	0.97	0.88–1.06	0.5
Age (per year increase)	1.07	1.04–1.11	<0.001				1.06	1.03–1.10	<0.001
NIHSS (per point increase)	1.06	0.95–1.19	0.3						
Hemoglobin, per mg/dL	0.88	0.72–1.07	0.2						
Presence of Inflammation	1.89	0.92–3.86	0.08				1.16	0.51–2.64	0.7

BMI, body mass index; ID, iron deficiency; NIHSS, National Institute of Health Stroke Scale. CI, confidence interval; OR, odds ratio.

3.2. Follow Up

One year after stroke (mean 382 ± 27 days), only 64 patients (46%) participated in the FU examination (FU cohort). Thus, 16 patients (11%) had problems traveling to the study center, 14 patients (10%) declined to continue the study, 6 patients (4%) had died, and 40 patients (29%) were lost to FU.

Comparing the entire study cohort with the FU cohort showed no difference in demographic, clinical, and biochemical parameters; stroke type and severity; comorbidities; and medication (Supplementary Materials Table S1).

3.2.1. Iron Status

At baseline, ID was found in 31 patients (52%) of the FU cohort (Figure 1B). This proportion increased up to 77% at FU examination ($p = 0.001$, Figure 1B). According to the ID subtypes, the proportion of patients with ID type I in this cohort increased from 36% to 49% and patients with ID type II from 13% to 28% ($p < 0.05$) from baseline to FU, respectively. All of the female patients that participated in the FU examination (38%) were found to have ID.

3.2.2. Muscle Strength

Patients with ID remained with lower HGS at FU (mean 28.8 ± 12.0 vs. 44.5 ± 8.4 kg, $p < 0.001$, Figure 3A) and in a sensitivity analysis performed in male patients only (mean 37.1 ± 9.9 vs. 44.5 ± 8.4 kg, $p < 0.05$).

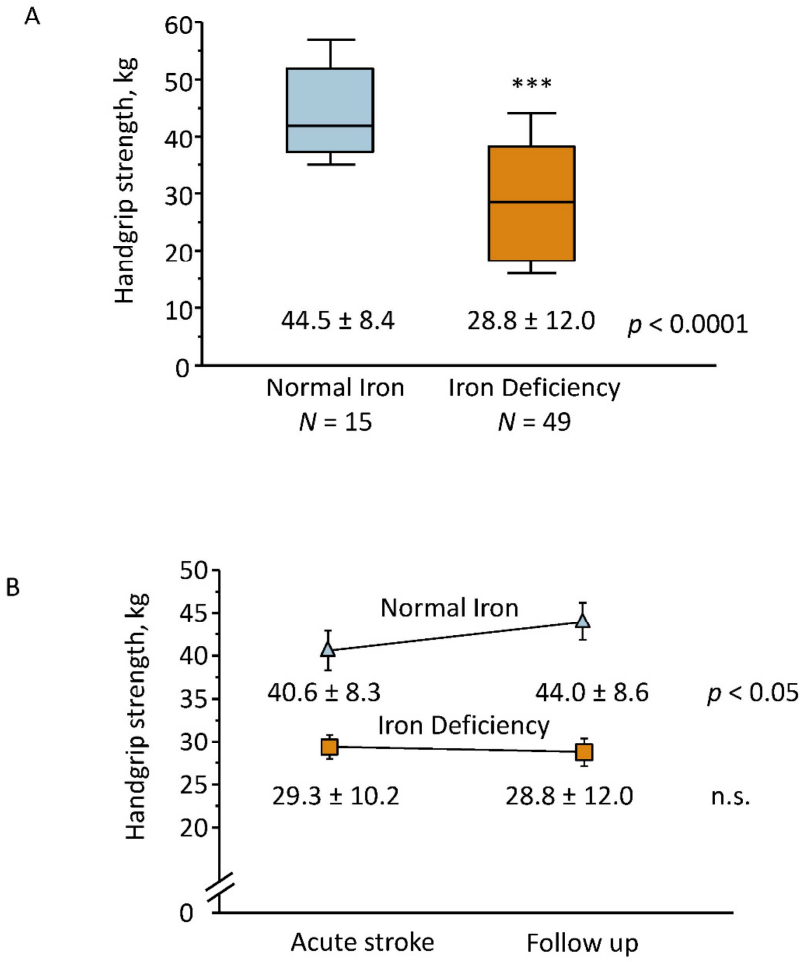

Figure 3. Handgrip strength at one-year follow up in patients with normal iron status (Normal Iron) and with iron deficiency (**A**). Changes in handgrip strength in patients with normal iron status (Normal Iron) and with iron deficiency (ID) within one year of follow up (**B**). n.s., non-significant. *** $p < 0.001$ vs. Normal Iron.

While patients with normal iron status showed an improvement of HGS at FU compared to baseline (mean 40.6 ± 8.3 vs. 44.0 ± 8.6 kg, $p < 0.05$), no improvement was observed in patients with ID (mean 29.3 ± 10.2 vs. 28.8 ± 12.0 kg, n.s., Figure 3B). The improvement of HGS was associated with normal iron status at FU (OR 3.7 [95% CI 1.01–13.5], $p < 0.05$).

3.2.3. Nutritional Status

Patients who developed ID at FU were found to have reduced appetite at baseline (mean 6.4 ± 2.1 vs. 7.6 ± 1.6, $p = 0.05$). At FU, patients with ID had more frequently low nutritional status compared to patients with normal iron status (49% vs. 20%, $p < 0.05$).

3.2.4. Logistic Regression Analyses of Handgrip Strength at Follow Up

In this restricted number of patients in the FU cohort, we found a trend in association between low HGS and reduced iron status. In invariable logistic regression analyses, ID, ID II, and TSAT < 20% all showed trends towards an association with low HGS (Table 3).

Table 3. Univariable logistic regression analyses applying low handgrip strength as a dependent variable at FU.

Parameter	OR	95% CI	*p*
		Univariate	
Transferrin saturation < 20%	2.86	0.97–8.42	0.06
Presence of ID	3.0	0.91–9.91	0.07
Presence of ID I	2.59	0.73–9.25	0.1
Presence of ID II	3.9	0.91–16.8	0.07
BMI (per kg/m^2 increase)	0.92	0.82–1.04	0.2
Age (per year increase)	1.08	1.02–1.14	<0.001
Hemoglobin, per mg/dL	0.98	0.75–1.29	0.9
Presence of Inflammation	4.69	0.94–23.3	0.06

BMI, body mass index; ID, iron deficiency.

4. Discussion

Up to date, ID in patients with stroke has not been recognized as relevant clinical complication that might affect the clinical outcome. This study shows a high prevalence of ID, and an association with low muscle strength in patients with acute ischemic stroke. The main findings of this study are as follows: (1) the prevalence of ID was high in patients with acute ischemic stroke and even increased within one year after the acute event; (2) patients with ID had lower muscle strength after stroke; (3) patients with ID remained with lower muscle strength one year after stroke; and (4) while patients with normal iron status showed an improvement in muscle strength at FU, such an improvement of muscle strength was not observed in patients with ID.

The present study investigated the longitudinal changes in ID in patients after stroke. We observed no spontaneous improvement of iron status within one year after stroke but rather an increase in ID prevalence. To date, we lack longitudinal studies on development of ID in patients after stroke. The majority of clinical studies investigating ID in patients with acute and chronic diseases report ID prevalence obtained as a cross-sectional value only. Previously, a longitudinal multicenter clinical trial investigating an association between ID and unspecific inflammation in otherwise healthy adults showed a 12% increase to 39% in prevalence of ID within three years in community-dwelling older individuals [24]. Previous observations in patients with acute conditions, including acute exacerbation of chronic obstructive pulmonary disease, acute coronary syndrome, or acute HF, reported a prevalence of ID ranging between 20% and 80% [25–27]. In patients with chronic conditions, such as chronic heart failure, pulmonary arterial hypertension, or cancer, the prevalence of ID ranged between 30% and 50% [13,28–30]. Therefore, our results fit into the range of ID prevalence described for other chronic conditions. However, further studies are warranted to validate our observations.

4.1. ID Categories in Stroke

We investigated the distribution of ID categories in patients with acute and chronic stroke since a difference in the prevalence of both ID subtypes has been found in cardio-oncology patients and patients with acute and chronic heart failure [21,27,29,31]. In the present study, ID type I, defined by ferritin levels < 100 suggesting depleted iron stores, was most prevalent. The proportion of patients with this type of ID increased by 12% within one year of stroke. The main causes of iron store depletion are excessive blood loss and inadequate dietary iron uptake or absorption [11,12]. Acute blood loss in the context of acute ischemic stroke is not considered relevant for exploration of the ID in these patients. Since ID might develop as a consequence of malnutrition [31], we investigated appetite and nutritional status of patients in acute and chronic stroke. Dysphagia and eating-related difficulties due to disability are frequently observed after stroke [32,33]. None of the patients included in our study had eating difficulties secondary to stroke event. However, patients who developed ID during FU were found to have the lowest appetite in

acute stroke and showed the lowest nutritional status upon FU examination. In addition, prescribed medications, including aspirin and proton pump inhibitors, might contribute to the depletion of iron stores [12]. Thus, in renal transplant recipients it was observed that the use of proton pump inhibitors was associated with ID and low ferritin levels independently of potential confounders [34]. In our study, almost 90% of patients in the FU cohort received aspirin for the secondary stroke prevention, and more than 20% of patients received proton pump inhibitors, which may explain the high prevalence of ID type I in the present study.

About one third of the patients with ID were found with ID type II, which is characterized by impaired iron metabolism triggered by systemic inflammation [35]. Indeed, we observed in these patients elevated C-reactive protein serum levels and white blood cell counts, indicating inflammation. We also found these patients to have reduced appetite and lower nutritional status one year after stroke.

In the present study, ID type I was found as a predominant mechanism of ID in patients with stroke. This is in line with previous reports, which observed this type of ID as a more frequent mechanism of ID in patients with cardio-oncologic diseases and patients with heart failure [27,28,36,37]. A recent prospective multicenter trial investigating about 700 patients with acute HF reported a predominance of ID type I and its persistence after treatment of acute HF [37]. The causes leading to the onset of ID type I in chronic stroke might include an inadequate iron uptake due to dietary habits and low appetite, as well as intake of medications, e.g., aspirin and proton pump inhibitors. ID type II is commonly observed in inflammatory condition in both clinical and experimental settings [11,12]. This type of ID is also expected in patients with underlying chronic comorbidities [12]. Our study is in line with these reports, as patients with inflammatory levels more often had ID type II, whereas patients without inflammation more often had ID type I. The therapeutic consequences of ID treatment depend on the underlying mechanism. While for the treatment and prevention of iron deficiency with low tissue iron stores (type I), parenteral iron supplementation, improved nutrition, and treatment of malabsorption may be considered, patients with ID type II should be treated for inflammation first [12]. Further investigations exploring the mechanisms of ID and the effects of iron supplementation on muscle recovery and outcome in acute and chronic stroke should be carried out.

4.2. Physical Performance and Muscle Strength

Lower physical performance has been reported in patients with ID and chronic diseases [6–8]. Patients with ID in the present study had a lower muscle strength assessed by handgrip and quadriceps muscle strength tests. Importantly, stroke severity according to the NIHSS and mRS was similar in patients with ID and without ID. ID patients with TSAT < 20% more often had low HGS. Notably, this cutoff has been shown to reflect ID in the bone marrow as assessed by bone marrow biopsies in patients with chronic HF [38]. TSAT < 20% is considered as a pathophysiological marker of reduced peripheral iron availability in all organs, including cardiac and skeletal muscle [39]. Our findings suggest that this could contribute to lower HGS in the present cohort.

We also found lower HGS in patients with ID at FU. Notably, we observed that patients without ID improved in HGS one year after stroke, whereas patients with ID did not show significant improvement.

The present results are consistent with the previous clinical trial demonstrating low physical capacity and worse clinical outcomes in the presence of ID during post-stroke rehabilitation [40].

4.3. Study Limitations

The present study has several limitations. This is a small-size prospective observational study including only patients with ischemic stroke with mild to moderate stroke severity. However, the study allowed the analysis of clinical and functional parameters in relation to ID, its prevalence, and different mechanisms of ID after stroke.

5. Conclusions

The present study showed that a significant proportion of patients with acute ischemic stroke present with iron deficiency. This ID is associated with lower muscle strength in acute and chronic stroke. ID might be underdiagnosed in patients with stroke. Assessment of iron status should be regularly performed in patients with stroke in order to diagnose and treat ID.

Supplementary Materials: The following supporting information can be downloaded at https://www.mdpi.com/article/10.3390/jcm11030595/s1. Table S1. Comparison in clinical characteristic of the entire cohort and follow-up (FU) cohort at baseline. Table S2. Baseline clinical characteristics of patients available to the clinical follow up examination one year after stroke according to presence of iron deficiency (ID) at follow up. Table S3. Short physical performance battery (SPPB) at baseline in the study groups.

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Data Availability Statement: The data presented in this study are available on request from the corresponding author. The data are not publicity available due to privacy.

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2.4 Frührehabilitation nach Schlaganfall: Beziehung zwischen der Herzratenvariabilität und funktionellem Ergebnis.

Scherbakov N*, *Barkhudaryan A*, Ebner N, von Haehling S, Anker SD, Joebges M, Doehner W. Early rehabilitation after stroke: relationship between the heart rate variability and functional outcome. ESC Heart Fail. 2020;7:2983-2991. (*geteilte Erstautorenschaft)*

Eine Reihe von metabolischen Komorbiditäten kann die klinische Prognose und das funktionelle Ergebnis von Patienten nach Schlaganfall beeinflussen. Autonome vegetative Dysfunktion im Akutstadium nach Schlaganfall ist prädiktiv für eine schlechtere klinische Prognose [108]. Klinische und experimentelle Studien berichten von vegetativer kardialer Dysfunktion mit insuffizienter Herzfrequenz- und Blutdruckregulation, Verminderung der Auswurffunktion und strukturellen Veränderungen des Myokardes nach Schlaganfall [54,109]. Das Ziel dieser Arbeit war die Auswirkung der Herzratenvariabilität (HRV, Heart Rate Variability) als Parameter der autonomen kardialen Regulation auf das funktionelle Ergebnis nach Abschluss der stationären Frührehabilitation nach Schlaganfall zu untersuchen.

In dieser prospektiven Studie wurden 103 Patienten mit ischämischen und hämorrhagischen Schlaganfall untersucht. Die Parameter der HRV (Standard Deviation of N-N Intervals, SDNN, und Triangularindex, TI) wurden im 24 Stunden Holter-Elektrokardiogramm (EKG) bestimmt. Die sympathische Überaktivierung wurde durch HRV-TI ≤ 20 definiert. Die Holter-EKGs wurden bei Aufnahme (23 ± 17 Tage nach Schlaganfall) in die Frührehabilitation erhoben. Der neurologisch-funktionelle Status wurde bei Aufnahme und nach vier Wochen bei Entlassung anhand der modified Rankin Scale (mRS), dem Barthel Index (BI) und der Rivermead Motor Assessment (RMA) Skalen bestimmt. Der funktionelle Outcome wurde als kumulative funktionelle Beeinträchtigung (CFD, Cumulative Funktional Disability), definiert und durch eine Summe von mRS ≥ 4, BI ≤ 70, RMA ≤ 5, gemessen. Anhand der HRV-TI hatten 80 Patienten eine normale autonome Funktion und 23 Patienten zeigten eine sympathische Überaktivierung.

Wie erwartet haben wir eine Verbesserung des funktionellen Status bei Entlassung feststellen können, wobei die Patienten mit normaler autonomer Funktion einen signifikant höheren Anstieg von neurologischen Indizes zeigten. Trotzdem wurde die Präsenz von CFD bei jedem fünften Patienten bei Entlassung nachgewiesen. Die Prävalenz von CFD verringerte sich von 40% bei der Aufnahme auf 28%, p=0.05 in der Gruppe mit normaler autonomer Funktion, während die Gruppe

mit der sympathischen Überaktivierung diesbezüglich keine signifikante Veränderung in der Prävalenz der CFD (14% vs. 16%) zeigte. Die logistische Regressionsanalyse nach multivariabler Adjustierung ergab eine signifikante Assoziation zwischen der CFD und der sympathischen Überaktivierung (OR 4,6 [95%CI 1.42-14,92], $p<0.05$) bei Entlassung.
Die Studie zeigte eine Assoziation zwischen der autonomen kardialen Dysfunktion mit eingeschränktem funktionellen Zustand nach stationärer Frührehabilitation bei Patienten nach Schlaganfall. HRV als nicht-invasiver Marker autonomer kardialer Regulation kann zusätzliche Information für die Beurteilung des funktionellen Outcomes bei Patienten mit Schlaganfall liefern.

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ORIGINAL RESEARCH ARTICLE

Early rehabilitation after stroke: relationship between the heart rate variability and functional outcome

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Abstract

Aims Impaired autonomic nervous system regulation is frequently observed in patients with stroke. The aim of this prospective study was to evaluate the impact of cardiac autonomic tone on functional outcome after the early post-stroke rehabilitation.

Methods and results One hundred and three consecutive patients (67 ± 11 years, body mass index (BMI) 27.1 ± 5.4 kg/m^2, 64% men) with ischaemic (84% of patients) and haemorrhagic stroke were studied. Depressed heart rate variability (HRV), as a surrogate marker of increased sympathetic tone, was defined by the standard deviation of NN intervals < 100 ms and HRV triangular index ≤ 20 assessed from a 24 h Holter electrocardiogram at admission to rehabilitation (23 ± 16 days after stroke). Twenty-two per cent of patients had depressed HRV at baseline and were comparable with patients with normal HRV with regard to their functional [Barthel Index (BI), modified Rankin Scale (mRS), and Rivermead Motor Assessment (RMA)] and biochemical status. After a 4-week follow-up, 70% of patients with depressed HRV showed a cumulative functional disability, defined by mRS ≥ 4, BI ≤ 70, and RMA ≤ 5, in contrast to patients with normal HRV (35%, $P = 0.003$). Patients with depressed HRV showed a worse functional status by BI (−16%, $P < 0.001$), RMA (−12%, $P < 0.05$), and mRS (+16%, $P < 0.01$), compared with patients with normal HRV. Cumulative functional disability was associated with depressed HRV (odds ratio 4.25, 95% confidence interval 1.56–11.54, $P < 0.005$) after adjustment for age, sex, and body mass index (odds ratio 4.6, 95% confidence interval 1.42–14.97, $P < 0.05$).

Conclusions The presence of autonomic cardiovascular dysregulation in patients with subacute stroke was associated with adverse functional outcome after the early post-stroke rehabilitation.

Keywords Stroke; Heart rate variability; Rehabilitation; Functional outcome

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Introduction

Stroke is a leading cause of disability in the adult age worldwide.[1] Early post-stroke rehabilitation plays an important role in recovery after stroke. A wide range of medical complications, including autonomic imbalance, characterized by decreased vagal modulation and increased sympathetic activation may influence the efficacy of rehabilitation efforts.[2,3] There is an evidence of cardiac dysfunction after clinical and experimental stroke.[4,5,6] A cardiac autonomic dysregulation, manifested by an impaired control of blood pressure and heart rate leading to cerebral hypoperfusion and secondary brain injury, may result in the increased susceptibility for post-stroke complications and contribute to an unfavourable functional outcome.[5,7,8] Previous studies have described the development of

autonomic imbalance in stroke patients using the analysis of heart rate variability (HRV).[9]

The presence of abnormal HRV in patients with stroke has been associated with adverse neurological outcome, post-stroke disability, and all-cause mortality.[10,11,12] In addition, the adverse impact of autonomic dysfunction, manifested by impaired HRV, on the progression of ventricular remodeling[13] and cardiovascular mortality has been reported in chronic heart failure (HF) and myocardial infarction,[14] and targeting this parameter by various therapeutic interventions has shown to improve outcomes in these patients.[15,16,17] Furthermore, the neuromodulation therapy, including vagus nerve stimulation, spinal cord stimulation, and baroreflex activation therapy, has recently received an interest to restore sympathovagal balance in patients with chronic HF.[18]

The effect of cardiovascular autonomic dysfunction on the clinical outcome of stroke patients after administration of the neurological rehabilitation has not been sufficiently investigated. The aim of this prospective study was to evaluate the impact of HRV on the functional outcome of patients with subacute stroke undergoing a hospitalized post-stroke rehabilitation programme.

Methods

Patient population

One hundred and forty-six patients with the diagnosis of acute ischaemic and haemorrhagic stroke admitted to the neurological rehabilitation centre Brandenburgklinik Bernau, Germany from April 2010 to August 2013 were consecutively enrolled into this prospective observational study. Forty-three (29%) patients with permanent atrial fibrillation were preliminary excluded from the analysis. The study patients underwent an individually adjusted early post-stroke rehabilitation programme according to the national standards for rehabilitation procedures after stroke. During the hospitalized rehabilitation, all patients were on individually adjusted standard medical therapy, including anticoagulants, antiplatelet drugs, beta-blockers, Ca channel antagonists, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, diuretics, and statins. Exclusion criteria were the presence of acute and chronic inflammatory disease, acute HF, myocardial infarction, liver cirrhosis, acute renal failure, immunosuppressive therapy, and a history of cancer within the past 5 years. The local ethics committee approved the study protocol, and all participants gave a written informed consent.

Determination of heart rate variability

Baseline two-channel 24 h Holter electrocardiogram (ECG) recordings (CardioDay®, Getemed, Teltow, Germany) were performed at admission to the rehabilitation centre. The HRV was determined using the parameters of time-domain, standard deviation of NN intervals (SDNN), and HRV triangular index. The presence of cardiac autonomic dysfunction in patients with stroke was revealed by depressed HRV,[19,20] which was defined by SDNN < 100 ms and HRV triangular index $\leq$ 20 according to the Guidelines of the European Society of Cardiology (ESC) and the North American Society of Pacing and Electrophysiology.[21]

Assessment of the neurological status and functional capacity

The evaluation of neurological status and functional examinations was performed at admission (baseline) and at discharge from the rehabilitation centre after a 4-week follow-up (FU).

Determination of the cumulative functional disability (CFD) included the assessment of functional status by three neurological scales.

The Barthel Index (BI) contains 10 basic activities of daily living related to self-care and mobility with scores ranging from '0' to '100', where the lower scores indicate greater dependency.[22]

The modified Rankin Scale (mRS) measures physical independence by the assessment of body function, activity, and participation in daily tasks on a scale ranging from '0' (no symptoms) to '5' (bedridden and fully dependent).

The Rivermead Motor Assessment (RMA) gross function subscale consists of scores from '1' to '13', which correspond to a range of physical activities increasing in complexity from 'turning over in bed' to 'hop on the affected leg 5 times'.[23]

Cumulative functional disability was present, if BI $\leq$ 70, mRS $\geq$ 4, and RMA $\leq$ 5.

Short physical performance battery and handgrip strength

Short physical performance battery (SPPB) included examinations of standing ability with both feet together in the side-by-side, semi-tandem, and tandem positions, time of walking 3 m, and time to rise 5 times from the chair and return to the seated position. The score ranges from 0 (not attended) to 12 points (completed).[24] The gait speed of the study patients was determined from the time of walking 3 m.

Isometric muscle strength of the hand was assessed by the handgrip strength test using a handgrip dynamometer (Saehan Corporation, Korea). The highest of three measurements was used for the analysis.

Quality of life and nutritional status

The quality of life was assessed by the European Quality of Life–Five Dimensions (EQ-5D) visual analogue scale, which ranges from '0' to '100', with a higher score indicating better health.[25]

Appetite was assessed by the visual analogue scale ranging from '0' (no appetite) to '10' (very good appetite).[26] The body mass index (BMI) was calculated as a ratio of body weight to height squared (kg/m^2).

Blood samples

Venous blood samples were obtained under standardized conditions after overnight fasting. Standard biochemical parameters were determined in a routine laboratory setting.

Statistical analysis

All data were presented as mean ± standard deviation, median [interquartile range (IQR)], or percentage. All variables were tested for normal distribution using the Kolmogorov–Smirnov test. Non-normally distributed data were log-transformed to achieve a normal distribution where indicated. Statistical comparisons were made using unpaired Student's *t*-tests, analysis of covariance adjusted for baseline, or Mann–Whitney *U*-test as appropriate. χ^2 test was used to assess categorical distribution between the study groups. Logistic regression analyses were used as appropriate. A value of $P < 0.05$ was considered statistically significant. Statistical analyses were performed with the StatView 5.0 software package (SAS Institute Inc., Cary, NC) and the GraphPad Prism 6.0 software.

Results

Baseline clinical characteristics of the study patients upon admission to the rehabilitation centre (23 ± 17 days after stroke) are presented in *Table 1*. The mean stroke severity according to the mRS was 3.7 ± 0.8, whereas no differences were observed between patients with ischaemic (81% of patients) and haemorrhagic stroke. Sixteen per cent of all patients (2 women and 14 men) had chronic HF (*Table 1*).

The analyses of 24-hour Holter ECG data revealed 23 (22%) patients with depressed HRV upon admission to the rehabilitation. On the basis of the values of HRV, the entire cohort was divided into two subgroups: patients with normal HRV and patients with depressed HRV. There were no significant differences between the study groups with regard to their baseline demographic, biochemical, and clinical parameters, except for heart rate, physical performance, and the prevalence of co-morbidities (*Table 1*).

Functional outcome after a 4-week follow-up

The improvement of physical and functional status was observed in all study patients after the hospitalized rehabilitation as manifested by an increase in the BI score by 28%, mRS by 14%, and RMA by 25% (*Figure 1A*, *C*, and *E*).

After adjustment for baseline, the functional outcome improved more significantly in patients with normal HRV compared with patients with depressed HRV. This improvement was observed by an increase in the BI score (median change 32% vs. 8%, $P = 0.054$), mRS (mean change 14% vs. 4%, $P = 0.013$), and RMA (median change 32% vs. 20%, not significant) in the two groups, respectively (*Figure 1A*, *C*, and *E*). Therefore, patients with depressed HRV remained with a worse physical status compared with patients with normal HRV according to the BI score (62 ± 24 vs. 76 ± 20, $P < 0.0001$), mRS (3.1 ± 1.0 vs. 3.7 ± 0.7, $P < 0.001$), and RMA (7.5 ± 2.5 vs. 6.4 ± 2.2, $P < 0.01$, all respectively) (*Figure 1B*, *D*, and *F*).

Short physical performance battery and handgrip strength

The number of patients who participated in the SPPB after a 4-week FU approximately doubled in the entire cohort compared with baseline (43% vs. 22%, $P = 0.001$). A significant improvement in the SPPB score was observed in patients with normal HRV in contrast to patients with depressed HRV (*Figure 2A*). No difference in gait speed was observed between the two subgroups after 4 week FU (*Figure 2B*). Although the number of patients who participated in a 3-meter walk test quadrupled compared with baseline, only 31 patients (30%) were able to perform the gait test.

Handgrip strength improved more significantly in patients with normal HRV compared to patients with depressed HRV after a 4-week FU [median change 12.9 (IQR 4.7–30.2) kg vs. 7.1 (IQR −3.8 to 19.2) kg, $P < 0.05$, respectively] (*Figure 2C*).

The cumulative functional disability

The CFD reduced from 54% of patients at baseline to 44% of patients after a 4-week FU ($P < 0.01$). However, a strong trend in the decrease of CFD prevalence was observed only in patients with normal HRV (40% vs. 28%, $P = 0.05$) (*Figure 3*).

After a 4-week FU, the CFD was associated with depressed HRV [odds ratio (OR) 4.25, 95% confidence interval (CI) 1.56–11.54, $P < 0.005$] after adjustment for age, sex, and BMI (OR 4.6, 95% CI 1.42–14.97, $P < 0.05$). Other baseline factors associated with CFD were age >65 years (OR 2.83, 95% CI 1.24–6.46, $P < 0.05$), BMI (OR 1.12, 95% CI 1.03–1.21, $P < 0.01$), the level of haemoglobin (OR 0.61, 95% CI 0.4–0.94, $P < 0.05$), and quality of life assessed by

Table 1 Baseline characteristics of study population

Parameter	All patients (N = 103)	Patients with normal HRV (N = 80)	Patients with depressed HRV (N = 23)	P value
Age, years	67 ± 11	67 ± 11	69 ± 13	0.7
Body mass index, kg/m^2	27.1 ± 5.4	26.8 ± 5.3	27.9 ± 5.9	0.4
Male sex *n*, %	88/60	73/62	15/52	0.3
Systolic blood pressure, mmHg	129 ± 15	130 ± 15	127 ± 18	0.5
Diastolic blood pressure, mmHg	78 ± 11	79 ± 10	76 ± 13	0.2
Mean blood pressure, mmHg	95 ± 11	96 ± 10	93 ± 13	0.2
Heart rate, b.p.m.	72 ± 11	69 ± 10	80 ± 12	<0.0001
Stroke severity				
Time after stroke, days	23 ± 17	22 ± 15	26 ± 24	0.4
Duration of rehabilitation, days	26 ± 6	27 ± 7	26 ± 5	0.6
Ischaemic stroke, *n* (%)	83 (81)	65 (81)	18 (78)	0.2
Cumulative functional disability, *n* (%)	54 (52)	40 (50)	14 (61)	0.4
Barthel Index	57 ± 23	58 ± 22	53 ± 26	0.3
Modified Rankin Scale	3.7 ± 0.8	3.6 ± 0.8	3.9 ± 0.7	0.2
Rivermead Motor Assessment	5.4 ± 2.3	5.5 ± 2.3	5.1 ± 1.9	0.5
Caregiver status				
Independent at home, *n* (%)	70 (69)	56 (71)	14 (64)	0.4
With help at home, *n* (%)	30 (30)	22 (28)	8 (36)	0.5
Nursing home, *n* (%)	1 (1)	1 (1)	—	
Quality of life, EQ-5D	49 ± 18	51 ± 17	48 ± 20	0.5
Appetite according to VAS	6.7 ± 2.0	6.8 ± 2.1	6.2 ± 1.9	0.2
Short physical performance battery	2.1 ± 3.3	2.2. ± 3.4	1.8 ± 3.1	0.5
Co-morbidities				
Diabetes mellitus, *n* (%)	58 (60)	48 (41)	10 (35)	0.5
Arterial hypertension, *n* (%)	91(88)	71 (89)	20 (87)	0.8
Dyslipidaemia, *n* (%)	64 (67)	49 (65)	15 (71)	0.7
Coronary artery disease, *n* (%)	32 (31)	24 (30)	8 (35)	0.7
Chronic heart failure, *n* (%)	16 (16)	12 (15)	4 (17)	0.9
Medication				
Anticoagulants, *n* (%)	73 (71)	57 (71)	16 (70)	0.9
Antiplatelet drugs, % (*n*)	70 (67)	53 (66)	17 (74)	0.5
β_1-selective blocker, % (*n*)	52 (51)	40 (50)	12 (52)	0.9
β_1-blocker equivalence dose[a]	4.3 ± 2.4	4.6 ± 2.6	3.3 ± 0.1	0.1
Ca channel antagonists, % (*n*)	34 (33)	26 (32)	8 (35)	0.8
ACE-I, % (*n*)	62 (60)	46 (58)	16 (70)	0.3
Angiotensin receptor blockers, % (*n*)	16 (16)	14 (18)	2 (9)	0.3
Diuretics, % (*n*)	44 (42)	32 (40)	12 (52)	0.3
Statins, % (*n*)	74 (72)	57 (71)	17 (74)	0.8
Biochemistry				
C-reactive protein, mg/L [IQR]	5.2 [1.7–8.3]	5.3 [1.8–8.4]	4.4 [1.3–8.2]	0.5
Haemoglobin, mmol/L	8.2 ± 1.0	8.3 ± 1.0	8.1 ± 1.0	0.2
Creatinine, mg/dL	1.0 ± 0.8	1.1 ± 0.7	0.8 ± 0.4	0.2

ACE-I, angiotensin-converting enzyme inhibitors; EQ-5D, European Quality of Life–Five Dimensions visual analogue scale; HRV, heart rate variability; IQR, interquartile range; VAS, visual analogue scale.
[a]β_1-blocker equivalence dose '1' correspond to 23.75 mg metoprolol or 1.25 mg bisoprolol or 1.25 mg nebivilol.

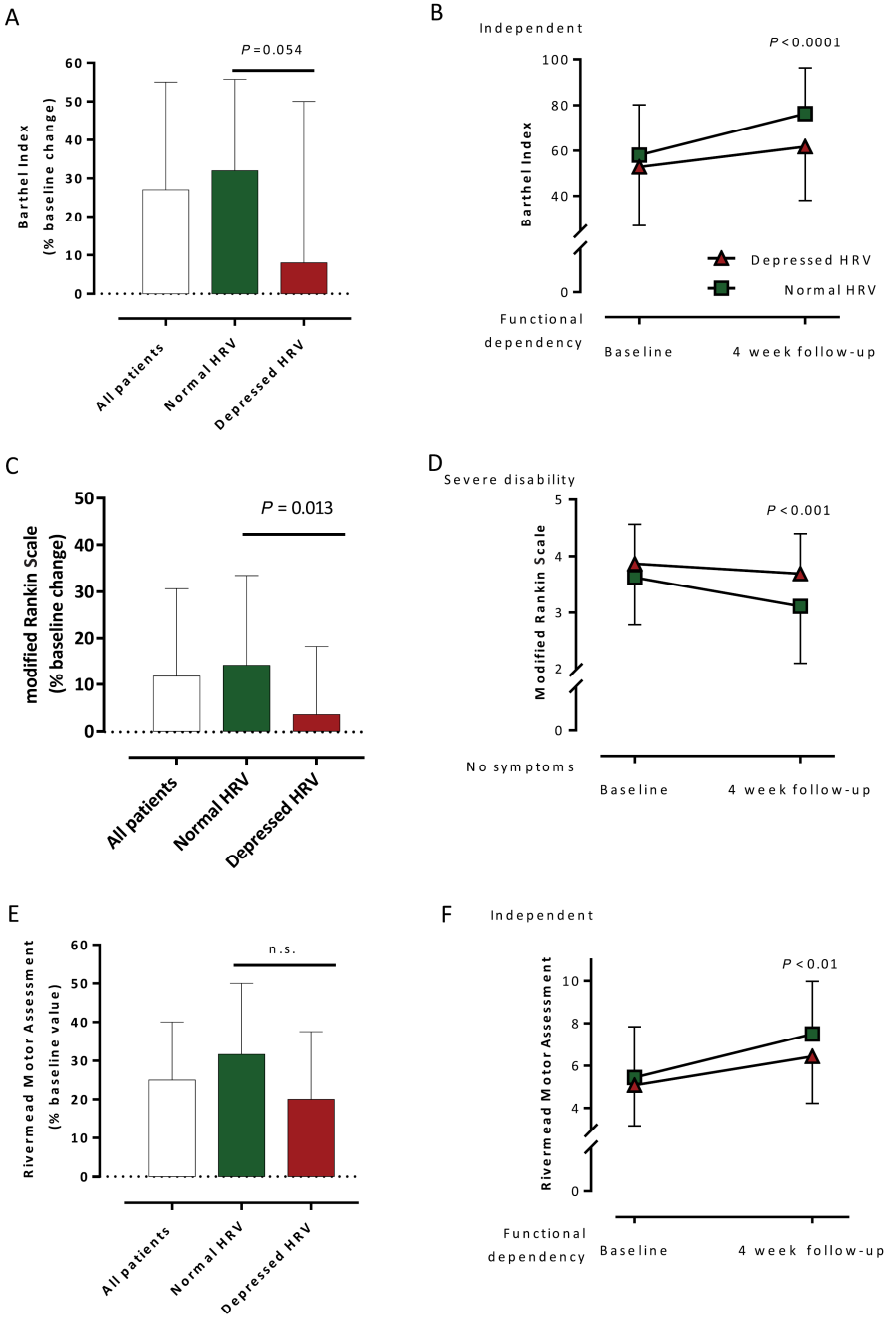
the European Quality of Life–Five Dimensions visual analogue scale (OR 0.96, 95% CI 0.94–0.99, P < 0.01) (*Table 2*). No significant associations of CFD with chronic HF (OR 0.77, 95% CI 0.26–3.32, P = 0.7) (*Table 2*) or other co-morbidities, except for a trend in association with diabetes mellitus (OR 2.08, 95% CI 0.925–4.68, P = 0.08), were observed.

Discussion

The main finding of the current study was the presence of autonomic cardiovascular dysregulation found in every fifth patient 3 weeks after stroke. The cardiac autonomic imbalance evaluated by HRV had a negative impact on the extent of functional performance following the early post-stroke rehabilitation.

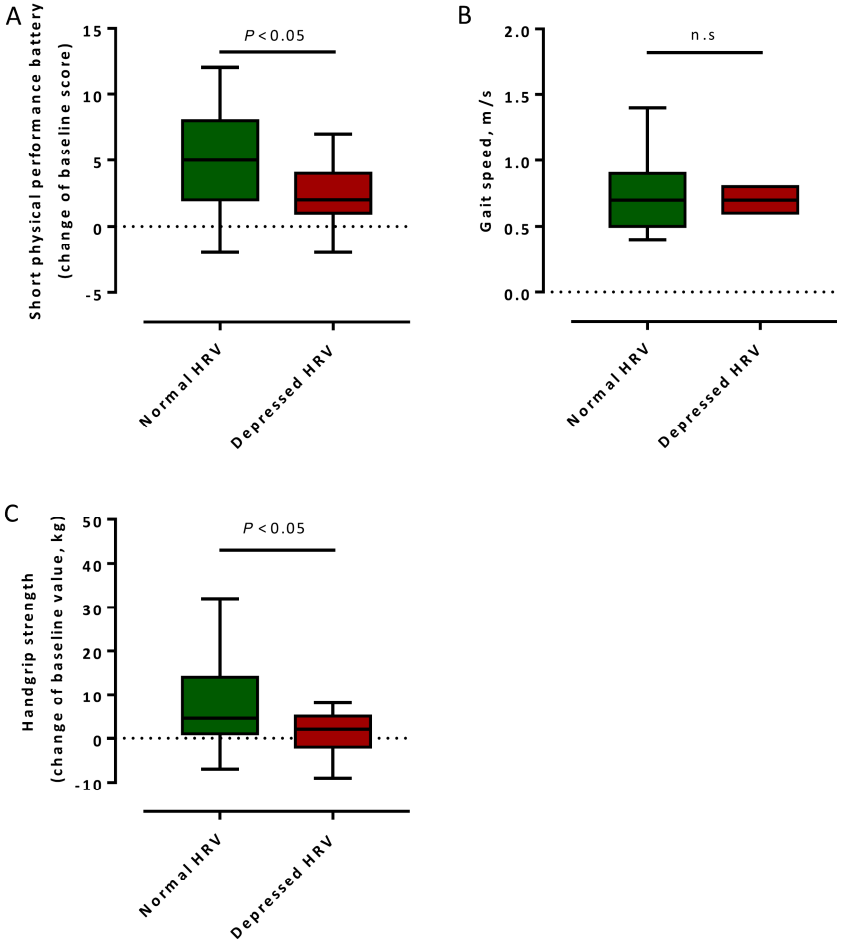
Our results are in line with recent clinical trials showing an association between cardiac autonomic control and cognitive performance or rehabilitation outcomes.[27,28] Previously, an association between SDNN and BI was observed after rehabilitation.[29] Furthermore, HRV was suggested as a marker of functional recovery after stroke.[30] We observed a higher prevalence of CFD in patients with depressed HRV after rehabilitation suggesting an association between cardiac autonomic function and efficacy of rehabilitation after stroke.

FIGURE 1 The percentage of baseline change after a 4-week follow-up in the entire patient cohort and in patients with normal heart rate variability (HRV) vs. patients with depressed HRV, as well as the physical performance at baseline and after a 4-week follow-up according to (A and B) Barthel Index, (C and D) modified Rankin Scale, and (E and F) Rivermead Motor Assessment gross function subscale. n.s., not significant.



This association was present even after adjustment for age, sex, and BMI, which confirms the results of previous clinical studies indicating the adverse effect of central autonomic derangement on the level of neurological recovery, physical, and functional outcome of patients with stroke.[3,4,11,20] In contrast, neurological deterioration was sought to be a cause of increased sympathetic activity in patients with acute stroke undergoing early mobilization.[31] However, in our study,

FIGURE 2 The change from baseline value in the (A) short physical performance battery, (B) gait speed, and (C) handgrip strength in patients with normal vs. depressed heart rate variability (HRV). n.s., not significant.



neurological and functional status was similar at the beginning of rehabilitation in both groups, suggesting the unfavourable impact of cardiac autonomic dysregulation on clinical outcome.

A previous study reported significant blood pressure fluctuations in the acute phase of different subtypes of non-cardioembolic ischaemic stroke resulting from autonomic dysfunction, characterized by sympathetic hyperactivity and a decrease in parasympathetic nervous system activity.[32] In contrast, the results of the present study did not show any differences in the blood pressure control between patients with normal and depressed HRV. However, our study did not investigate different subtypes of stroke. Vice versa, we aimed to identify relevant clinical parameters equally to patients with all stroke subtypes admitted to the early post-stroke rehabilitation.

In the present study, we assessed the functional outcome using a combined endpoint of CFD. We dichotomized the outcome assessed by all three scales to address an overall functional state, which included the evaluation of body function, physical activities, mobility, self-care, and global functional health of the study patients. The clinical significance of a composite assessment to evaluate the outcome in acute stroke was previously shown.[33] In addition, implementation of composite endpoints resulted in an improvement of the clinical trial efficiency and lower sample size for trials investigating minor ischaemic stroke.[34]

We performed the assessment of SPPB in the current study, which is widely used in geriatric medicine to assess frailty, sarcopenia, and lower extremity function in older persons.[35,36,37] The results have shown that only 22% of all stroke patients at baseline and 43% of patients after a

FIGURE 3 The distribution of patients with normal functional capacity vs. cumulative functional disability (CFD) in the subgroups of patients with normal vs. depressed heart rate variability (HRV) at baseline and after a 4 week follow-up (FU).

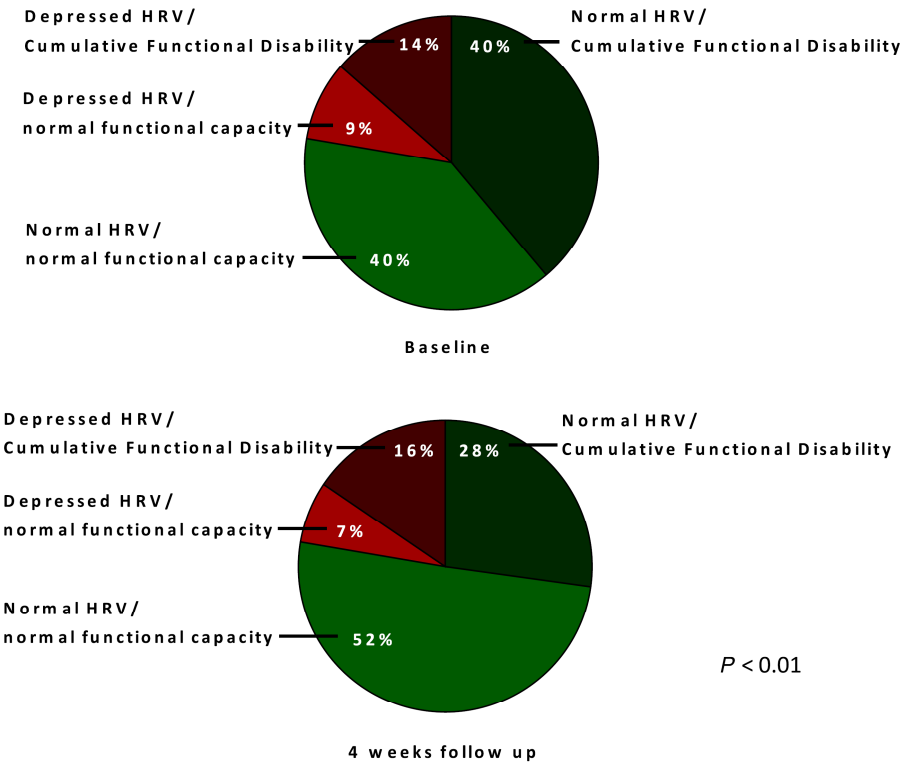


Table 2 Baseline clinical parameters associated with cumulative functional disability in patients with stroke after a 4-week follow-up

Parameter	OR [95% CI]	*P* value	OR [95% CI]	*P* value
Depressed HRV	4.25 [1.56–11.54]	<0.005	4.6 [1.42–14.97]	<0.05
Age >65 years	2.83 [1.24–6.46]	<0.05	3.12 [1.16–8.41]	<0.05
Ischaemic stroke	2.53 [0.75–8.51]	0.1		
Diabetes mellitus	2.08 [0.925–4.68]	0.08	1.4 [0.51–3.85]	0.5
Dyslipidaemia	2.07 [0.85–5.05]	0.1		
C-reactive protein, per log (mg/L)	2.04 [0.98–4.25]	0.6		
Arterial hypertension	1.57 [0.44–5.58]	0.5		
β_1-selective blocker	1.34 [0.61–2.97]	0.5		
Body mass index, kg/m^2	1.12 [1.03–1.21]	0.008	1.12 [1.02–1.24]	<0.05
Coronary artery disease	0.88 [0.38–2.06]	0.8		
Age, per year	1.05 [1.03–1.08]	<0.05		
Heart rate, per 10 beats	1.07 [0.75–1.52]	0.7		
Quality of life, EQ-5D	0.96 [0.94–0.99]	0.004	0.96 [0.93–0.99]	<0.01
Duration of rehabilitation (days)	0.95 [0.89–1.02]	0.2		
Appetite according to VAS	0.90 [0.74–1.1]	0.3		
Chronic heart failure	0.77 [0.26–3.32]	0.7		
Haemoglobin, mmol/L	0.61 [0.4–0.94]	0.02	0.61 [0.36–1.03]	0.06
Male sex	0.58 [0.26–1.30]	0.2	1.02 [0.37–2.80]	1.0

CI, confidence interval; EQ-5D, European Quality of Life–Five Dimensions visual analogue scale; HRV, heart rate variability; OR, odds ratio; VAS, visual analogue scale.

4-week FU were able to perform the test. Among them, only 30% of patients were able to complete a 3-meter walk test at FU. However, because of the high prevalence of paresis in these patients, the results did not differ between the two groups. The low participation rate of the study population was due to the coordination deficit in patients with paretic

limbs, which indicated a relevant floor effect of SPPB in this study cohort.[38,39]

Thus, considering that inadequate physical performance observed in patients with depressed HRV after the early rehabilitation is regarded as an indicator of a poor recovery following acute stroke, the findings of the present study particularly underline the clinical significance of targeting cardiovascular autonomic dysfunction to improve the efficacy of treatment, quality of life, and survival of patients with acute stroke. In general, in view of the evidence that autonomic dysfunction also has an important role in the progression of chronic HF, the results of the present study also emphasize the importance of targeting autonomic cardiovascular dysregulation in patients with chronic HF who develop acute stroke, which may lead to acute decompensation of HF, physical disability, and increased mortality. Therefore, treatment of cardiac autonomic derangement by various therapeutic approaches may improve the functional performance and efficacy of HF therapy and decrease the risk of future cerebrovascular events in these patients. In conclusion, this study provides a perspective for future clinical trials evaluating the impact of cardiac autonomic dysregulation on the functional outcome after the early rehabilitation in HF patients with subacute stroke.

Study limitations

The present study is limited by a relatively small sample size. However, in comparison with similar studies[22,23,24], our study remained with the largest patient number. The prescribed medications, such as beta-blockers or angiotensin-converting enzyme inhibitors, may affect the interpretation of autonomic test results[40,41]; however, we did not observe a difference in the prescription of these medications between the two patient subgroups. The presence of co-morbidities, such as diabetes mellitus, has been described to influence HRV[42]. In the current study, this effect was observed as a trend.

Conclusions

The present study has demonstrated an association between autonomic cardiovascular dysregulation with adverse rehabilitation outcome and dependency in patients with subacute stroke. These findings suggest that HRV, as a non-invasive ECG marker, may provide additional information for evaluation of clinical recovery following the hospitalized neurological rehabilitation. Patients with depressed HRV may require an extensive reconditioning treatment with a long-term FU to enhance the physical performance after acute stroke. A wide spectrum of specific training programmes applied in sport and for treatment of psychiatric disorders or metabolic diseases have shown to improve HRV.[43,44] Therefore, randomized clinical trials investigating the effect of a non-pharmacological treatment of cardiovascular autonomic dysfunction on the functional outcome of patients with stroke are warranted.

Conflict of interest

The authors have no conflict of interest to declare.

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2.5 Schlafbezogene Atemstörung bei Patienten mit akutem Schlaganfall: eine pathophysiologische Verbindung zur peripheren endothelialen Dysfunktion

***Scherbakov N**, Sandek A, Ebner N, Valentova M, Nave AH, Jankowska EA, Schefold JC, von Haehling S, Anker SD, Fietze I, Fiebach JB, Haeusler KG, Doehner W. J Am Heart Assoc. 2017;6:e006010.*

Die schlafbezogene Atemstörung (sleep-disordered breathing, SDB) tritt häufig nach Schlaganfall auf und wird als Ausdruck autonomer Dysfunktion gewertet. Es wird angenommen, dass eine gestörte Empfindlichkeit des Atemzentrums in der Medulla oblongata gegenüber Kohlendioxid eine Hyperventilation und Hypokapnie verursacht, die vom Körper mithilfe von Cheyne-Stokes-Atmung mit periodisch auftretenden Apnoen kompensiert wird. Eine weitere Komorbidität die nach Schlaganfall als Ausdruck der autonomen Dysfunktion gedeutet wird ist die periphere endotheliale Dysfunktion. In der vorliegenden Studie untersuchten wir den Zusammenhang zwischen dem SDB und der endothelialen Funktion im Akutstadium und ein Jahr nach Schlaganfall. In die Studie wurden 101 Patienten (mittleres Alter 69 Jahre, 61% Männer, mittleres NIHSS Score 4) mit akutem ischämischen Schlaganfall im Versorgungsgebiet der MCA eingeschlossen. Die Studienuntersuchungen wurden im Akutstadium (Baseline, BL) und ein Jahr nach Schlaganfall (1y Follow up, FU) durchgeführt. Die FU-Kohorte zählte 41 Patient. SDB wurde als Apnoe-Hypopnoe-Index, AHI≥5 Episoden/Stunde definiert und mittels transthorokaler Impedanzanalyse bestimmt. Periphere endotheliale Funktion wurde anhand des reaktiven Hyperämie Index (RHI) mittels EndoPat2000 Fingerplethysmographie gemessen. Neurologisches Defizit, funktioneller und körperlicher Status wurde anhand von NIHSS, mRS und Barthel Index erhoben.

Bei 57% der Patienten (N 58) bei BL wurde eine SDB festgestellt. Patienten mit SDB hatten signifikant höhere neurologische Defizite (Median NIHSS 5 vs. 3, p=0.007) und schwerere körperliche und funktionelle Beeinträchtigungen im Vergleich zu Patienten ohne SDB (mRS: 2.8±1.6 vs. 1.8±1.1, P<0.001, Barthel Index: 64±37 vs. 80±25, p<0.05). Die periphere endotheliale Dysfunktion wurde bei diesen Patienten doppelt so häufig im Vergleich zu Patienten ohne SDB festgestellt (64% vs. 32%, P<0,01). In der FU- Kohorte verringerte sich die Prävalenz der SDB von 59% auf 15%, P<0.001. Vor allem Patienten mit normalisierter Schlafatmung zeigten auch eine verbesserte periphere endotheliale Funktion (RHI 2,0 ±0,6 vs. 1.7±0.3, P<0,05). Die sechs Patienten mit erhaltener SDB hatten einen rechtshirnigen Infarkt.

Diese Studie zeigt einen Zusammenhang zwischen der SDB und peripherer endothelialen Dysfunktion bei Patienten mit Schlaganfall als Ausdruck einer vegetativen Dysregulation. Es wurde ein transienter Charakter der SDB bei Patienten mit leichtem bis mittelgradigem neurologischen Defizit festgestellt. Eine Normalisierung der SDB ist mit Verbesserung der peripheren Endothelfunktion verbunden.

ORIGINAL RESEARCH

Sleep-Disordered Breathing in Acute Ischemic Stroke: A Mechanistic Link to Peripheral Endothelial Dysfunction

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***Background*—**Sleep-disordered breathing (SDB) after acute ischemic stroke is frequent and may be linked to stroke-induced autonomic imbalance. In the present study, the interaction between SDB and peripheral endothelial dysfunction (ED) was investigated in patients with acute ischemic stroke and at 1-year follow-up.

***Methods and Results*—**SDB was assessed by transthoracic impedance records in 101 patients with acute ischemic stroke (mean age, 69 years; 61% men; median National Institutes of Health Stroke Scale, 4) while being on the stroke unit. SDB was defined by apnea-hypopnea index ≥5 episodes per hour. Peripheral endothelial function was assessed using peripheral arterial tonometry (EndoPAT-2000). ED was defined by reactive hyperemia index ≤1.8. Forty-one stroke patients underwent 1-year follow-up (390±24 days) after stroke. SDB was observed in 57% patients with acute ischemic stroke. Compared with patients without SDB, ED was more prevalent in patients with SDB (32% versus 64%; $P<0.01$). After adjustment for multiple confounders, presence of SDB remained independently associated with ED (odds ratio, 3.1; [95% confidence interval, 1.2–7.9]; $P<0.05$). After 1 year, the prevalence of SDB decreased from 59% to 15% ($P<0.001$). Interestingly, peripheral endothelial function improved in stroke patients with normalized SDB, compared with patients with persisting SDB ($P<0.05$).

***Conclusions*—**SDB was present in more than half of all patients with acute ischemic stroke and was independently associated with peripheral ED. Normalized ED in patients with normalized breathing pattern 1 year after stroke suggests a mechanistic link between SDB and ED.

***Clinical Trial Registration*—**URL: https://drks-neu.uniklinik-freiburg.de. Unique identifier: DRKS00000514. **(*J Am Heart Assoc.* 2017;6:e006010. DOI: 10.1161/JAHA.117.006010.)**

Key Words: clinical trial • endothelial dysfunction • sleep disorders • sympathetic nervous system

Sleep-disordered breathing (SDB), including obstructive sleep apnea and central sleep apnea, is frequently observed in patients with cardiovascular diseases or stroke.[1] SDB is characterized by periodic breathing frequency and depth. The prolonged episodes of breathing cessation lead to hypoxia, hypercapnia, and sympathetic activation, subsequently increasing the risk for cardiovascular events.[2] Several clinical studies observed an association of obstructive sleep apnea—caused by the collapse of upper airways—with systemic inflammation, atrial fibrillation, (recurrent) stroke, and heart failure.[3,4]

Compared with wakefulness, natural sleep is associated with increased carbon dioxide pressure in blood.[5] After cerebral stroke, an impaired sensitivity of the medullary respiratory center to carbon dioxide leads to relative hyperventilation and subsequent to hypocapnia.[6] Therefore, nocturnal as well as diurnal periodic breathing (eg, Cheyne–Stoke respiration) with episodes of hypoxia and hypercapnia might serve as a compensatory mechanism for normalization of carbon dioxide pressure.[7] Indeed, nocturnal hypocapnia was independently associated with Cheyne–Stoke respiration after stroke.[6] In addition, input from the cerebral cortex has been suggested as a suppresser of periodic pathological breathing patterns, generated in the brainstem. Therefore, the loss of

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Clinical Perspective

What Is New?

- Our observational study demonstrates an association of peripheral endothelial dysfunction with sleep-disordered breathing in patients with acute ischemic stroke.
- Normalization of sleep-disordered breathing pattern 1 year after stroke was associated with improved endothelial function.

What Are the Clinical Implications?

- Whereas sleep-disordered breathing is a frequent finding in the acute phase of stroke, our study suggests a transient character of SDB in the majority of stroke patients with mild-to-moderate neurological deficit on admission.
- Large, prospective stroke studies including a systematic screening for sleep-disordered breathing and endothelial dysfunction are needed to assess an impact on the frequency of cerebrovascular and cardiovascular complications.

the cortical control on the brainstem after brain injury might be causal for central sleep apnea.

SDB is accompanied by increased sympathetic activation. The most common manifestations of autonomic dysfunction observed in association with acute stroke are cardiac arrhythmias, changes of heart rate variability, fluctuations of blood pressure, endothelial dysfunction (ED), and myocardial injury.[8–12] Previously, we reported the presence of peripheral ED in patients with acute ischemic stroke.[13] However, only a few studies investigated an association between SDB and ED in stroke.[14,15]

We hypothesized that nocturnal SDB after acute ischemic stroke may contribute to development of peripheral ED. Subsequently, we prospectively examined patients in the acute phase after ischemic stroke and 1 year afterward.

Patients and Methods

The Study Protocol

The present analysis is a part of the prospective, single-center observational BoSSS (Body Size in Stroke Study; German registry for clinical trials number DRKS00000514), performed at the stroke unit (Charité–Medical School, Berlin, Germany).

One hundred one consecutive patients (aged 35–89 years) with acute ischemic stroke of the middle cerebral artery territory were recruited to this study within 48 hours after symptom onset. In the acute phase after stroke, patients were treated according to the current guidelines recommendations individually adjusted (including antiplatelet drugs, statins, angiotensin-converting enzyme inhibitors, and β-blocker). Thirty-one patients (31%) received thrombolytic therapy (Actilyse; Boehringer Ingelheim, Ingelheim am Rhein, Germany) according to the appropriate therapeutic window.

The study protocol has been published previously.[16] Briefly, inclusion criteria were: age ≥21 years; presence of acute ischemic stroke within the middle cerebral artery territory; and neurological deficit according to the National Institutes of Health Stroke Scale (NIHSS) ≤12. Exclusion criteria were acute and chronic inflammatory diseases, immune suppressive therapy, history of cancer shorter than 5 years, and women with known pregnancy.

The protocol was approved by the Charité Ethics Committee, and written informed consent was obtained from all subjects.

Baseline Examinations

Baseline examinations were completed in-hospital in the acute phase after stroke. Stroke-related neurological deficit was evaluated by the NIHSS and estimation of ischemic brain injury volume was assessed using the Alberta Stroke Program Early CT score.[17] Functional impairment and disability were evaluated by the modified Rankin Scale (mRS) and the Barthel Index (BI). Venous blood samples were obtained under standardized conditions after overnight fasting. Standard biochemical parameters were assessed immediately in the routine clinical laboratory. Body mass index was calculated as a ratio of body weight and squared height (kg/m²).

Assessment of SDB

Screening for SDB was performed 4±2 days after symptom onset using transthoracic impedance recording integrated into a Holter system (CardioDay; Getemed, Teltow, Germany). Analyses of SDB were performed visually as previously described.[18] Presence of SDB was defined by apnea-hypopnea index (AHI) ≥5 episodes per hour.[19]

Peripheral endothelial function

Quantitative determination of peripheral endothelial function was assessed by application of finger plethysmograph (EndoPAT2000; Itamar Medical, Caesarea, Israel) as described previously.[13] Assessments were performed 4±2 days after symptom onset under standardized conditions after at least 15 minutes of supine rest in a quiet, air-conditioned room. An estimation of endothelial function was based on peripheral arterial tonometry of the index finger of the nonparetic arm. A reactive hyperemia index (RHI) was defined as a ratio between the post- and preoccluded measurement of the peripheral arterial tonometry signal corrected for signal of the nonoccluded contralateral to the brain lesion arm. ED was considered with RHI ≤1.8.

Cardiovascular assessment

Echocardiographic evaluation of myocardial morphology and global left ventricular function was performed (Vivid S5 with 3S-RS 1.5–3.6 MHz transducer; GE Medical Systems, Marlborough, MA). Left ventricular ejection fraction (LVEF) was calculated according to the Simpson biplane method. Left ventricular diastolic dysfunction was determined according to the diagnostic criteria of the European Society of Cardiology: septal (<7 cm/s) or lateral (<10 cm/s) mitral annular early-diastolic (e′) peak velocity by pulsed-waved spectral tissue Doppler imaging and LVEF 50% to 55%.[20] Left ventricular systolic dysfunction was considered in patients with clinical sings of heart failure (HF) and LVEF ≤50%. Patients with normal LVEF (≥55%) and without clinical signs of HF were considered to have no HF.

One Year Follow-up

Repeated measurements of the baseline study examinations were conducted in 41 patients at 1-year follow-up (FU). Sixty patients were lost to FU.

Statistical Analysis

All data were presented as means± SD, median (interquartile range; IQR) or percentage, as appropriate. Data were tested for normal distribution using the Kolmogorov–Smirnov test. Statistical comparisons were made using paired or unpaired Student *t* tests or Mann–Whitney U test or Kruskal–Wallis test. The chi-squared test was used to assess categorical distribution between groups. Simple linear regression and Pearson correlation and uni- and multivariate logistic regression analyses were used, as appropriate. A $P<0.05$ was considered statistically significant. Statistical analyses were performed with the StatView software package (version 5.0; SAS Institute Inc, Cary, NC).

Results

One-hundred one patients with acute ischemic stroke (69±12 years; body mass index, 28.2±4.6 kg/m^2) were studied within 4±2 days after symptom onset. The study cohort consisted of 62 (61%) male and 39 female patients. Patients were mild to moderate disabled (median NIHSS, 4.0 [IQR, 2–7]; mean BI, 71±33; mean mRS, 2.3±1.5; Table 1). Median AHI in the entire study cohort was 5.7 [IQR, 3–13] episodes per hour. Baseline characteristics of all patients are given in Table 1.

Patients were divided according to the presence or absence of SDB. In 58 patients (57%), the presence of SDB was identified (median AHI, 11.6 [IQR, 7–18.25] episodes per hour). This subgroup consisted mainly of male patients (72%). Compared with patients without SDB, patients with SDB had more-severe neurological deficit according to the NIHSS (Figure 1A), larger infarct volume in approximation by Alberta Stroke Program Early CT score (Figure 1B), as well as higher functional impairment according to the mRS and BI (Figure 1C and 1D; Table 1). No further differences were observed regarding comorbidities or clinical and biochemical characteristics between both of the subgroups (Table 1).

Peripheral Endothelial Function in Relation to SDB After Acute Ischemic Stroke

Patients with SDB showed peripheral ED—as indicated by RHI—compared with patients without SDB (RHI 1.7±0.5 versus 2.0±0.4; $P=0.001$; Figure 2A). Peripheral ED was present in 64% of patients with SDB and in 32% of patients without SDB ($P=0.003$). ED was strongly associated with higher AHI in simple regression analysis ($r=-0.38$; $P<0.001$; Figure 2B). In univariate logistic regression, presence of SDB was associated with presence of peripheral ED (odds ratio [OR], 3.9 [95% confidential interval {CI}, 1.6–9.4]; $P=0.003$; Table 2). After adjustment for sex, age, and body mass index, the presence of SDB remained independently associated with the presence of ED (OR, 3.1 [CI, 1.2–7.9]; $P<0.05$).

Logistic Regression Analyses

In univariate logistic regression an association between the presence of SDB and neurological deficit according to the NIHSS (OR, 1.2 [95% CI, 1.1–1.4]; $P<0.01$), functional impairment according to the mRS (OR, 1.7 [95% CI, 1.2–2.3]; $P<0.001$) or to the BI (OR, 0.9 [95% CI 0.8–1.0]; $P<0.05$), and male sex (OR, 3.0 [95% CI, 1.3–6.9]; $P=0.01$) was found at baseline (Table 2). The stroke affected hemisphere, atrial fibrillation, and cardiac function (E/e′ ratio or LVEF) were not correlated with presence of SDB in the acute phase after ischemic stroke (Table 2).

Cardiac Function and SDB in Acute Stroke

Basic echocardiographic parameters were similar in patients with or without SDB (Table 3). Comparing stroke patients without HF (n=21) with patients with Left ventricular diastolic dysfunction (n=62) or those with left ventricular systolic dysfunction (n=18) revealed higher AHI in patients with left ventricular systolic dysfunction ($P=0.04$; Figure 3). No significant difference in SDB prevalence was observed between these groups (no HF, 43%; left ventricular diastolic dysfunction, 58%; left ventricular systolic dysfunction, 72%).

Table 1. Baseline Characteristics of Study Population

Clinical Parameter	All Patients (N=101)	Patients Without SDB (N=43)	Patients With SDB (N=58)	*P* Values
Age, y	69±12	68±13	69±11	0.7
Male sex, %	61	47	72	0.008
BMI, kg/m^2	28.2±4.6	28.7±5.7	27.8±3.5	0.3
Diastolic BP, mm Hg	80±14	81±15	79±13	0.5
Systolic BP, mm Hg	141±21	142±24	140±18	0.7
Thrombolytic therapy, %	31	23	21 (36)	0.2
AHI, episodes/h	5.7 [3–13]	2.5 [1–3]	11.6 [7–19]	<0.0001
Stroke severity				
ASPECT	8.4±1.4	8.9±1.1	8.1±1.6	0.007
NIHSS	4.0 [2–7]	3 [2–4]	5 [2.75–8]	0.01
NIHSS ≥5, %	41	23	53	0.002
Barthel Index	71±33	80±25	64±37	0.014
Modified Rankin	2.3±1.5	1.8±1.1	2.8±1.6	<0.001
Right hemispheric stroke, %	55	49	61	0.3
Medical history				
Atrial fibrillation, %	18	14	21	0.5
History of sleep apnea, %	2	…	3	…
Hypertension, %	69	61	76	0.1
Diabetes mellitus, %	26	21	29	0.4
Dyslipidemia, %	33	33	33	0.9
Biochemistry				
Hemoglobin, g/L	14.5±1.6	14.2±2.0	14.8±1.3	0.2
Glucose, mg/dL	112±42	115±47	109±38	0.5
HbA1C, mg/dL	6.1±1.1	6.2±1.3	5.9±0.9	0.2
Sodium, mmol/L	140.6±3.5	140.1±3.9	141.1±3.2	0.2
Potassium, mmol/L	4.0±0.4	4.1±0.4	4.0±0.5	0.3
Triglyceride, mg/dL	139±61	138±62	139±61	0.9
Cholesterol, mg/dL	185±44	191±46	178±43	0.1
Low-density lipoprotein, mg/dL	108±39	113±37	104±41	0.2
High-density lipoprotein, mg/dL	48.0±15.0	51.1±1 6.5	46.0±13.7	0.1
Creatinine, mg/dL	0.9±0.2	0.9±0.2	1.0±0.2	0.2
C-reactive protein, mg/dL	4.8 [2–8]	4.8 [2–8]	5.0 [2–9]	0.3
Uric acid, mg/dL	5.3±1.4	5.1±1.4	5.5±1.4	0.3

Values are mean±SD, median [interquartile range], or percentage. AHI indicates Apnea-hypopnea index; ASPECT, Alberta Stroke Program Early CT; BMI, body mass index; BP, blood pressure; HbA1C, hemoglobin A1C; NIHSS, National Institutes of Health Stroke Scale; SDB, sleep-disordered breathing.

SDB and Endothelial Function 1 Year After Ischemic Stroke

Clinical characteristics of 41 patients who were available at 1-year FU are given in Table 4. One year after stroke, 19 patients (46%) improved significantly their functional capacity according to the BI (delta BI, 27±21; *P*<0.001) compared to baseline, 18 (44%) remained unchanged, whereas 4 worsened their functional capacity (delta BI, −19±13; *P*=0.058). Furthermore, 63% of the patients revealed a body weight increase compared to baseline (delta body weight 6.2±5.6 kg; *P*=0.002), whereas 37% showed a body weight lost (delta body weight, −3.7±3.8 kg; *P*<0.0001). Prevalence of SDB decreased from 59% at baseline to 15% at

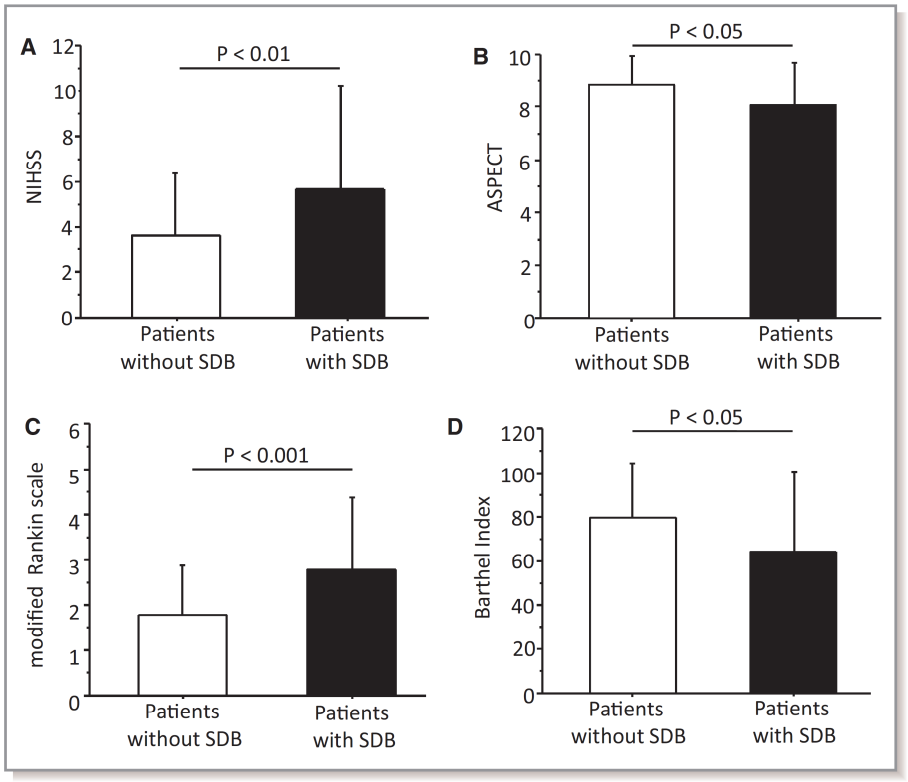

Figure 1. Neurological deficit at baseline according to the National Institutes of Health Stroke Scale (NIHSS); (A); estimation of stroke-related brain lesion according to the Alberta Stroke Program Early CT (ASPECT) score (B); functional impairment at baseline according to the modified Rankin scale (mRS) (C); functional disability at baseline according to the Barthel index (D) in patients without sleep-disordered breathing (SDB) compared with the patients with SDB.

1 year follow-up (P<0.001). Median AHI decreased from 7.1 [IQR, 3–13.75] episodes per hour at baseline to 2.15 [2–3.75] episodes per hour at 1-year FU (P<0.001). All 6 stroke patients with sustained SDB had right hemispheric middle cerebral artery stroke. Notably, only stroke patients with normalized nocturnal breathing pattern compared with baseline showed improved peripheral endothelial function after 1 year (RHI, 2.0±0.6 versus 1.7±0.3 at baseline, P=0.03, respectively; Figure 4). By contrast, patients with sustained SDB after 1 year still showed ED (RHI, 1.7±0.5 at FU versus 1.7±0.3 at baseline, P=0.9; Figure 4).

Discussion

The main findings of the present study are (1) the association of peripheral ED with presence of SDB in patients with acute stroke and (2) an improvement of peripheral endothelial function in a subset of study patients with recovery of SDB 1 year after ischemic stroke. Furthermore, we confirm earlier studies showing that SDB is frequently found in patients with acute ischemic stroke, particularly in those with moderate neurological deficit.

Influence of SDB on the Endothelial Function

We observed a strong association between presence of SDB and peripheral ED in the acute phase after ischemic stroke. Whereas ED belongs to established risk factors contributing to the development of cerebrovascular and cardiovascular diseases, ED was also found in around 30% of stroke patients without SBD in the acute phase after ischemic stroke. Increased sympathetic activation after stroke might lead to transient worsening of autonomic function.[11] Our results support this hypothesis by observing an improvement of endothelial function in patients who recovered from SDB 1 year after the index stroke, but not in those patients with persistent SDB. Our data support an association between the SBD and ED, because the presence of SDB remained independently associated with the peripheral ED (adjusted harzard ratio, 3.4 [95% CI, 1.27–9.01]).

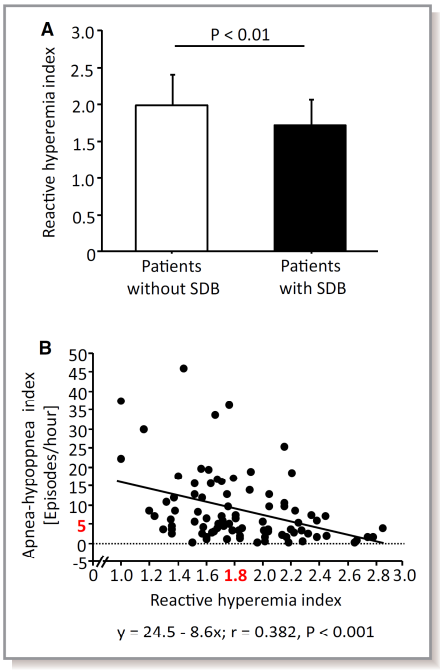

Figure 2. Peripheral endothelial function according to reactive hyperemia index (RHI) in patients without sleep-disordered breathing (SDB) and in those with SDB after acute ischemic stroke (A). Association between the peripheral endothelial function according to RHI and the severity of SDB according to apnea-hypopnea index (AHI) (B).

Table 2. Logistic Regression Analyses Between Presence of SDB and Clinical Variables

Parameter	OR	95% CI	*P* Value
Univariate analyses			
Reactive hyperemia index, per 0.1 point	0.15	0.05 to 0.51	0.002
Presence of endothelial dysfunction	3.57	1.49 to 8.58	0.004
NIHSS, per point	1.19	1.05 to 1.36	0.009
NIHSS ≥5	3.79	1.58 to 9.10	0.003
Barthel index, per 10 points	0.88	0.78 to 0.99	0.046
Modified Rankin Scale, per point	1.66	1.22 to 2.26	0.001
ASPECT, per point	0.62	0.43 to 0.89	0.01
Male sex	3.02	1.32 to 6.93	0.009
Lesion of right hemisphere	1.48	0.67 to 3.28	0.33
Atrial fibrillation	1.61	0.55 to 4.70	0.38
LVEF, per 5%	0.89	0.69 to 1.13	0.33
E/e′ ratio	1.00	0.92 to 1.09	0.92
Multivariate analyses (adjusted for age, sex, BMI)			
1. Reactive hyperemia index	0.17	0.05 to 0.60	0.006
2. Presence of endothelial dysfunction	3.09	1.21 to 7.87	0.018
3. Presence of endothelial dysfunction and NIHSS ≥5	17.6	2.18 to 142.3	0.007

ASPECT indicates Alberta Stroke Program Early CT; BMI, body mass index; CI, confidence interval; LVEF, left ventricular ejection fraction; NIHSS, National Institutes of Health Stroke Scale; OR, odds ratio; SDB, sleep-disordered breathing.

Peripheral vascular function has been analyzed in several studies before. Peripheral arterial tonometry techniques—based on the reactive hyperemia induced by forearm ischemia—enables noninvasive measurements of the peripheral endothelial function and correlates significantly with flow-mediated dilation of the brachial artery.[21] The measurement of endothelial function in the current study was performed on the index finger of the nonparetic arm. We therefore believe that the findings represent a systemic effect on endothelial function and are not biased by local effects of the paretic limb.

The association between ED and SDB has been shown in few studies.[22–24] However, a recent study stated an association of moderate and severe SDB with increased arterial stiffness in patients 3 months after stroke, but did not find an association with endothelial dysfunction.[15] Because repeated measurements in our study demonstrate a temporal course of an association, the delayed follow-up in the recent study may explain the respective findings. Our observations are in line with previous reports showing a temporal imbalance of autonomic nervous regulation that attenuates within days after acute stroke.[11] A recent meta-analysis demonstrated a clinically relevant improvement of endothelial function after treatment of OSA with continuous positive airway pressure, which is also in accord with our findings.[25]

SDB and Autonomic Dysfunction

Consistent with previous studies,[26,27] our study showed that stroke patients with SDB had more often severe stroke compared with those without SDB, whereas both patient groups were comparable regarding demographic and comorbidity status as well as metabolic, cardiac, and inflammatory characteristics. The association of SDB with neurological impairment might be related to stroke-associated autonomic vegetative imbalance. However, a previous study showed an association between severe stroke and progressive failure of cardiac autonomic function in 50 patients with ischemic stroke.[28] In our present study, the Alberta Stroke Program Early CT score at baseline—as an estimation of stroke volume—was associated with a higher prevalence of SDB. Furthermore, we observed an association between SDB and peripheral ED, potentially serving as a downstream surrogate marker of autonomic function.

Table 3. Basic Echocardiographic Characteristics of the Study Groups

Parameter	Patients Without SDB (N=43)	Patients With SDB (N=58)	*P* Values
HR, bpm	71±11	72±12	0.9
LVEF, %	57±7	56±10	0.3
LA diameter, mm	41.3±5.3	42.0±6.0	0.5
LV wall diastolic diameter, mm	11.1±2.3	11.5±2.2	0.5
LV diastolic diameter, mm	47.3±8.3	48.3±6.9	0.5
IVS diastolic diameter, mm	12.4±2.4	13.1±2.4	0.1
Septal e′ mitral annular velocity by TDI, cm/s	7.0±2.7	6.5±2.6	0.5
Lateral e′ mitral annular velocity by TDI, cm/s	8.9±3.2	7.4±2.6	0.1
E/e′ ratio	11±5	12±5	0.9
RA diameter, mm	38.0±7.5	35.4±8.4	0.3
RV diastolic diameter, mm	2.9±0.7	3.5±1.7	0.3
TAPSE, mm	23±6	22±5	0.3

Values are mean±standard deviation. bpm indicates beats per minute; HR, heart rate; IVS, intraventricular septum; LA, left atrial; LV, left ventricular; LVEF, left ventricular ejection fraction; RA, right atrial; RV, right ventricular; SDB, sleep-disordered breathing; TAPSE, tricuspid annular plane systolic excursion; TDI, tissue Doppler imaging.

Of note, other factors than impaired central control of vegetative regulation may contribute to ED in acute stroke as well. Previously, we have shown a role of the L-arginine/nitric oxide pathway in the peripheral endothelial function in patients with acute stroke, by observing elevated levels of asymmetric dimethylarginine, an endogenous inhibitor of nitric oxide synthesis, in parallel to stroke severity.[13]

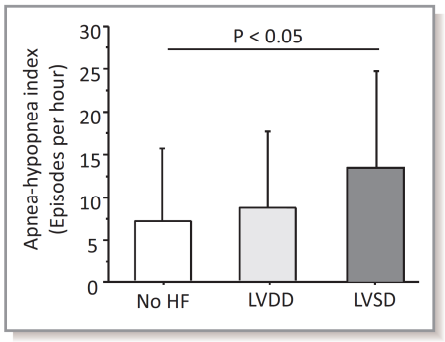

Figure 3. Severity of sleep-disordered breathing (SDB) according to apnea-hypopnea index (AHI) in patients without heart failure (HF), in those with left ventricular diastolic dysfunction (LVDD) and in those with left ventricular systolic dysfunction (LVSD).

Table 4. Clinical Characteristics of Patients Completed 1 Year FU Examinations

	Baseline (N=41)	1 Year FU (N=41)	*P* Values
Age, y	68±12	69±11	<0.001
BMI, kg/m²	27.6±4.0	28.5±4.5	0.03
Male sex, n (%)	28 (70)	28 (70)	…
Days after stroke	3±2	390±24	<0.001
Thrombolytic therapy, n (%)	11 (27)	…	…
Presence of SDB, n (%)	24 (58.5)	6 (14.6)	<0.001
AHI, episodes/h	7.0 [3–13]	2.15 [2–3.75]	<0.001
RHI	1.8±0.4	1.9±0.5	0.2
Barthel Index	80±27	93±17	0.001
Modified Rankin Scale	2.0±1.2	1.3±1.1	<0.001

AHI indicates apnea-hypopnea index; BMI, body mass index; FU, follow-up; RHI, reactive hyperemia index; SDB, sleep-disordered breathing.

SDB: A Potential Treatment Target After Stroke?

The question is whether patients should be treated for SDB in the acute phase of stroke. Based on the observed association in the present study, normalized breathing pattern may attenuate autonomic nervous imbalance and may hence prevent clinical complications such as arrhythmias, blood pressure peaks, or ED. Given the transient character of this neurovegetative imbalance, also, a temporary intervention may be effective.[11]

In contrast to these considerations, however, recent data put into question a potential benefit from augmented

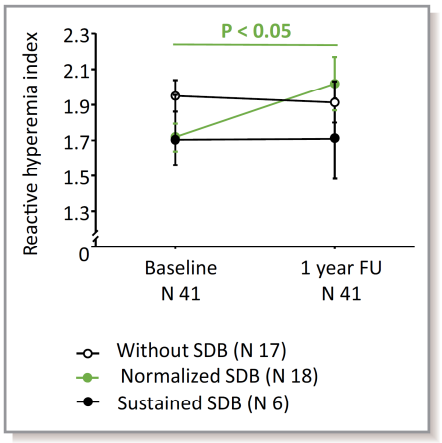

Figure 4. Peripheral endothelial function according to reactive hyperemia index (RHI) in the follow-up cohort at baseline and at 1-year follow-up examination. SDB indicates sleep-disordered breathing.

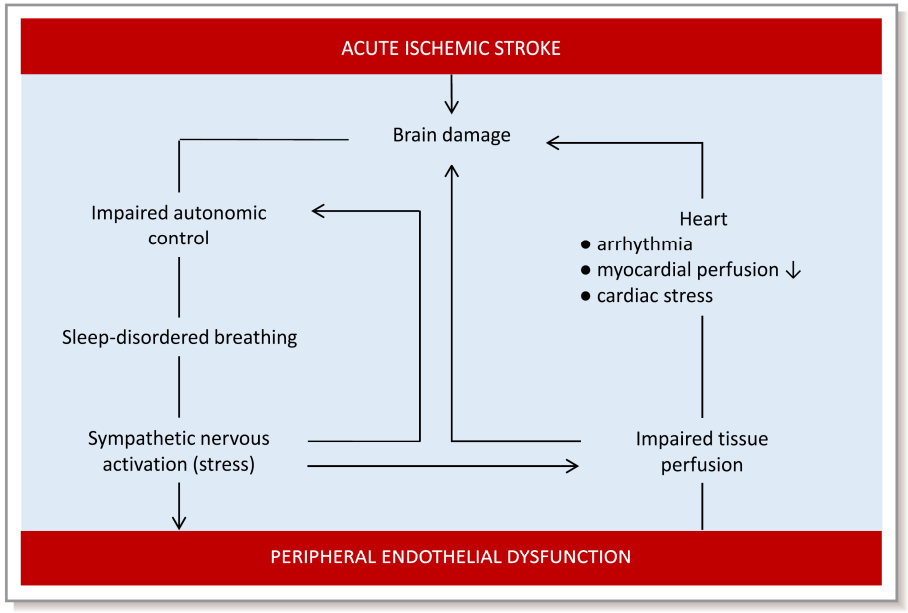

Figure 5. Interaction between acute ischemic stroke, sleep-disordered breathing, and peripheral endothelial dysfunction.

ventilation support therapy in the SDB. Considering Cheyne–Stoke respiration as a part of the compensatory mechanism in autonomic dysfunction,[6] manipulating this breathing pattern could be detrimental. Indeed, a recent large, randomized treatment trial (SERVE-HF [The Treatment of Predominant Central Sleep Apnoea by Adaptive Servo Ventilation in Patients With Heart Failure]) investigated the treatment of the SBD by adaptive servoventilation in patients with chronic HF with reduced ejection fraction showed an increased mortality in the intervention group.[29] The investigators hypothesized that distraction from the compensatory breathing pattern by the adaptive servo ventilation might be responsible for the adverse outcome in the study.

Notably, all patients with sustained SDB at 1-year FU in the present study suffered from a right hemispheric stroke. Both hemispheres are known to have a different influence on autonomic function, and increased sympathetic activity has been observed in right hemispheric stroke in experimental stroke models and in human stroke.[30]

There are some limitations of the present study. The study population was limited to patients with mild-to-moderate stroke. One could speculate that a more-pronounced mechanistic interaction may have been observed in patients with even more-severe stroke. Indeed, we detected only a small number of patients with severe SBD in this specific study population. This makes the founded changes in ED more remarkable. Furthermore, the detection of SDB was based on 1 parameter. The standard sleep apnea monitoring includes a minimum of 3 parameters: airflow, respiratory effort, and blood oxygenation.[31] Impedance is a known technique for detection of the thoracic effort, but does not allow distinguishing between central and obstructive breathing disorders. Furthermore, the calculated AHI is an estimation because sleep time was anamnestic collected. However, screening is feasible and accurate.[18,32] Another limitation was a small number of patients available for FU assessment. One year after stroke, all of the patients were contacted either by telephone or by mail and invited to 1-year FU. As a result, roughly 40% of the patients were able to come to the hospital. The analyses of patients who came to 1-year FU in comparison with the rest of the entire study cohort (age, 70±12 years; body mass index, 28.6±4.9 kg/m^2) revealed better physical performance (BI, 80±26 versus 64±35; P=0.016, and mRS, 2.0±1.2 versus 2.6±1.6; P=0.026, respectively) at baseline. Thus, moderate functional impairment and long-term disability might be causal for the high rate of loss to FU in the present study.

Conclusions

This study explores an interaction between ischemic stroke, SDB, and peripheral ED (Figure 5). This is an important observation, which identifies a modifiable risk factor, and even a potential therapeutic target. Acute ischemic stroke is accompanied by a high prevalence of SDB, probably attributed to loss of cortical control and autonomic nervous system

imbalance. Whereas SDB was transient in a subset of stroke patients, peripheral ED—as a surrogate marker of autonomic dysfunction—was associated with the presence of SDB after acute ischemic stroke and during the clinical course. Further studies are needed to analyze an impact of SDB in patients with ischemic stroke.

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Disclosures

None.

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3 Diskussion

In den hier vorgelegten Arbeiten haben wir die schlaganfallassoziierten metabolisch bedingten Komorbiditäten und deren Auswirkungen auf den klinischen Status bei Patienten mit Schlaganfall im akuten, subakuten und chronischen Stadium systematisch untersucht. Es konnte folgendes gezeigt werden,

- die Gewichtsveränderungen nach Schlaganfall sind häufig; ein Jahr nach Schlaganfall entwickelten 21% der Patienten eine Kachexie. Die kachektischen Patienten verblieben mit niedrigstem funktionellen Status;
- C-terminales Fragment des Agrin-Proteins, CAF22, kann als Biomarker für das Monitoring der Veränderung der Muskelmasse hilfreich sein. Die dynamischen Veränderungen des Plasmaspiegels von CAF 22 waren mit der Änderung der Muskelkraft und Muskelmasse während der stationären Frührehabilitation bei Patienten nach Schlaganfall assoziiert;
- 48% der Patienten im Akutstadium nach Schlaganfall und 77% der Patienten im chronischem Stadium hatten einen Eisenmangel. Patienten mit Eisenmangel hatten eine verringerte Muskelkraft und einen niedrigeren funktionellen Status;
- eine autonome kardiale Dysregulation anhand der HRV Parameter als Ausdruck der sympathischen Überaktivierung im subakuten Stadium nach Schlaganfall wurde festgestellt. Es bestand ein Zusammenhang zwischen der autonomen Dysregulation und einem eingeschränkten funktionellen Zustand nach stationärer Frührehabilitation.
- ein Zusammenhang zwischen den SDB und peripherer ED als Ausdruck einer Dysregulation des vegetativen Nervensystems wurde festgestellt. Es konnte ein transienter Charakter der SDB bei Patienten mit leichtem bis mittelgradigem Schwergrad des Schlaganfalls festgestellt werden. Eine Normalisierung der SDB war mit der Verbesserung der peripheren Endothelfunktion verbunden.

Schlaganfall betrifft jährlich 12 Millionen Menschen weltweit [8] und ca. 1,1 Million Menschen in Europa [110]. Die Prävalenz des Schlaganfalls hat sich 2019 im Vergleich mit 1990 fast verdoppelt und Patienten mit einem 1 Schlaganfall werden immer jünger [111]. So waren 2019 63% der Patienten mit Schlaganfall jünger als 70 Jahre [8].

Durch die Fortschritte in der Diagnostik und Behandlungsmöglichkeiten von akuten Schlaganfällen in den letzten Dekaden wurde die funktionelle Unabhängigkeit nach Schlaganfall zwar verbessert [112,113], jedoch wird eine steigende Anzahl der Patienten abhängig von der Schwere der neurologischen Ausfällen lebenslang eine Betreuung brauchen [114]. Daher ist die hausärztliche Nachversorgung von Patienten mit Schlaganfall inklusive effektive Rehabilitation eine relevante Behandlungskomponente. Sekundärprophylaxe nach ischämischen Schlaganfällen beruht auf medikamentöse Prävention von erneuten Schlaganfällen durch die symptomatische Behandlung kardiovaskulärer Risikofaktoren wie arterielle Hypertonie, VHF, Hypercholesterinämie, etc. [115], sowie eine Lebensstilmodifikation, Behandlung von Diabetes mellitus und obstruktiver Schlafapnoe [116].

Die Rolle der metabolischen Komplikationen und vegetativer Dysregulation nach Schlaganfall für die klinische Prognose wird zunehmend verstanden. Metabolische Komorbiditäten sind für den klinischen Verlauf und den Rehabilitationserfolg nach Schlaganfall relevant. Zu den bisher nicht direkt therapeutisch adressierten Komorbiditäten bei Schlaganfall gehören katabole Überaktivierung mit schlaganfallassoziierter Kachexie sowie Eisenmangel. Besonders diese Komorbiditäten sind im Fokus der vorliegenden interdisziplinären Forschungsarbeit.

3.1 Schlaganfallassoziierte Kachexie: pathophysiologische Aspekte

Die Ergebnisse unserer prospektiven Beobachtungsstudie zeigen, dass jeder fünfte Patient innerhalb von einem Jahr nach Schlaganfall eine Kachexie entwickelte. Die kachektischen Patienten hatten den niedrigsten funktionellen und physischen Status im Vergleich zu nicht-kachektischen Patienten. Für die Diagnosestellung der Kachexie benutzten wir diagnostische Kriterien wie Gewichtsverlust, niedrige Muskelmasse und Muskelkraft sowie erhöhte Entzündungsparameter [61]. Unsere Ergebnisse stimmen mit Ergebnissen anderer Studien überein, die Kachexie bei chronischen Erkrankungen wie CHI [117,118] oder COPD [119] untersucht haben. In diesen Studien lag die Prävalenz der Kachexie im Bereich von 15% bis 35%, außerdem konnte eine Assoziation zwischen der Kachexie und schlechter klinischer Prognose festgestellt werden.

Wir haben zwar nur eine Kohorte von Patienten mit leichten bis milden Schweregrad des Schlaganfalls anhand der NIHSS untersucht, dennoch deuten unsere Ergebnisse auf eine wichtige

Komorbidität die nach einem Schlaganfall auftreten kann. Den übermäßigen Körpergewichtsverlust, der mit einem reduzierten klinischen Status nach Schlaganfall assoziiert ist, kann man als Ausdruck einer katabolen Überaktivierung, die bei Patienten mit milden neurologischen Defiziten aufgetreten ist, sehen. Daher sind die regelmäßigen Gewichtskontrollen in der klinischen Praxis und bei der hausärztlichen Nachversorgung von Patienten nach Schlaganfall sehr wichtig. Gewichtsverlust ist die klinische Folge der komplexen systemischen metabolischen Mechanismen, die weiterer Aufklärung bedürfen.

3.1.1 Katabole Aktivierung

Ein Verlust des Körpergewichtes und der Muskelmasse bei Patienten mit Muskellähmungen nach Schlaganfall ist ein häufiger Befund [3,4]. Wir haben die Hypothese aufgestellt, dass der schlaganfallassoziierte Gewichtsverlust ein klinisches Symptom für die katabole Stoffwechsellage bei Patienten mit Schlaganfall ist. Aus unseren Untersuchungen geht hervor, dass der Gewichtsverlust bei kachektischen Patienten mit dem Schwund der Magermasse und des Fettgewebes verbunden ist. Im Gegensatz zu früheren Studien haben wir gezeigt, dass sowohl Muskelschwund als auch Verlust vom Fettgewebe ein systemischer Prozess ist, der den Gesamtkörper betrifft. Dieser Gewichtsverlust wurde nicht nur bei Patienten mit Muskellähmungen, sondern auch bei Patienten ohne motorische Defizite beobachtet. Im Einklang mit unseren Ergebnissen berichtet eine Studie von einem Muskelschwund bei 7% der Patienten ein bis drei Jahre nach Schlaganfall [120]. Zwar wurde in dieser Studie eine niedrigere Prävalenz der Sarkopenie als erwartet festgestellt, aber der höhere BMI nach Schlaganfall, leichtere neurologische Defizite und die erhaltene Gehfähigkeit der Patienten könnten die Gründer dafür sein [120].

Die experimentellen Studien haben die mechanistischen Zusammenhänge zwischen Schlaganfall und Gewichtsverlust aufgezeigt. In Untersuchungen am MCAO Mausmodell wurde eine erhöhte Aktivität der Caspase-3 und Caspase-6 in der Skelettmuskulatur sowohl ipsilateral als auch contralateral zur Hirnläsion der Extremität festgestellt [53]. Des Weiteren wurde eine erhöhte Aktivität von Trypsin-like, Peptidyl-Glutamyl-like und Chymotrypsin-like Aktivität in der Skelettmuskulatur beobachtet. Also zeigte das MCAO Mausmodell eine katabole Aktivierung in der Skelettmuskulatur nach Schlaganfall, die sich aus Apoptose (Caspase-Signaling) und proteolytischen

Muskelabbau (erhöhte Aktivität aller drei katalytischen Proteasomdomänen) zusammensetzte [53]. Zusätzlich wurde eine Gewichtsabnahme mit einem Maximum am dritten postoperativen Tag gezeigt [53]. Ähnliche Ergebnisse zeigten eine weitere Studie, die Kachexie anhand der metabolischen Veränderungen an isolierten Muskelzellen von Patienten mit CKD untersuchte [121]. In dieser Studie wurde eine erhöhte Proteindegradierung und eine Insulinresistenz in Bezug auf in vitro Proteinsynthese festgestellt. Die Drosselung der anabolen Aktivität wird vor allem durch die Insulinresistenz definiert [122].
Diese Resultate bekräftigen unsere Hypothese, dass ein Gewichtsverlust nach Schlaganfall vor allem als Ausdruck der katabolen Stoffwechsellage bewertet werden sollte [53,54].

3.1.2 Systemische Inflammation

Unsere Untersuchungen zeigen, dass bei kachektischen Patienten erhöhte Entzündungswerte im Vergleich zu nichtkachektischen Patienten zu registrieren waren. Die systemische Inflammation hat einen gestiegenen Grundumsatz zufolge, welcher die katabole Stoffwechsellage und damit eine Kachexie fördern kann.
Im Rahmen der vorliegenden Arbeiten konnten wir eine Assoziation zwischen systemischer Inflammation und CrP-Serumlevels mit Kachexie bei Patienten zeigen. Ein akuter Schlaganfall wird häufig von einer nicht-spezifischen Entzündungsreaktion als eine akute Antwort des Körpers zur Beseitigung der Gehirnschädigung begleitet [123,124]. Vor allem die Inflammationsmarker wie IL-6 und CrP sind der Gegenstand intensiver Untersuchungen. Die Studien zeigen Assoziationen zwischen den Entzündungsparametern und reduziertem klinischen Zustand und erhöhter Sterblichkeit nach Schlaganfall [125,126]. Es gibt zunehmend Hinweise, dass bei Patienten mit chronischen Erkrankungen niederschwellige systemische und lokale Inflammation zum Muskelschwund [127,128] und Kachexie [129] führt.
Inwiefern die systemische Inflammation für den in unseren Untersuchungen nachgewiesenen Muskelschwund und Gewichtsverlust nach Schlaganfall ursächlich gewesen sein ist derzeit nur zu vermuten. Zwar gibt die Copenhagen sarcopenia Study einen Hinweis auf eine Assoziation zwischen geringgradiger Inflammation und Muskelschwund, jedoch solle dieser Mechanismus nicht der Haupttreiber der altersassoziierten Sarkopenie sein [130]. Unsere Studie wurde als prospektive

klinische Beobachtungsstudie konzipiert, die die zugrundeliegenden pathophysiologischen Mechanismen nicht tiefer in ihren Einzelheiten untersuchte. Dies bleibt künftigen Studien mit anderen Studiendesign vorbehalten.

3.1.3 Ernährungsstatus

Unterernährung kann bei Patienten bereits im Akutstadium nach Schlaganfall auftreten [131]. Die schlaganfallbedingten Komplikationen wie Schluckstörungen oder Muskellähmungen (Hemi- oder Fazialisparese) können die Nahrungsaufnahme beeinträchtigen, was neben einen gestiegenen Grundumsatz auch negative Stickstoffbilanz und somit Kachexie begünstigen kann. Tatsächlich, ein Zusammenhang zwischen Muskellähmungen, Schluckstörungen und Kachexie wurde in anderen Studien aufgezeigt [132,133]. Unsere Ergebnisse zeigen den niedrigsten Appetit und demzufolge einen schlechteren Ernährungszustand bei kachektischen Patienten gegenüber anderen Patienten. Dysphagie ist hochprävalent nach Schlaganfall und kann bis zur Hälfte der Patienten betreffen [134]. Zwar haben wir keine Dysphagie bei unseren Patienten feststellen können, jedoch sahen wir einen reduzierten Appetit bei kachektischen Patienten sowie eine Assoziation zwischen Appetitverbesserung und einer Gewichtszunahme nach einem Jahr. Auch das Serumalbumin, Marker des Ernährungszustandes, war am niedrigsten in der kachektischen Gruppe im Vergleich zu Patienten mit konstanten Gewicht oder Gewichtszunahme. Wir können davon ausgehen, dass der verminderte Appetit und systemische Inflammation zur Malnutrition und Kachexie führten. Abgesehen von neurologischen Ausfällen und Malnutrition könnten auch soziale Faktoren wie Aktivitätseinschränkungen, Schwierigkeiten beim Lebensmitteleinkauf oder Essenszubereitung eine Rolle spielen und einen reduzierten Ernährungsstatus sowie die Entwicklung der Kachexie befördern [135].

3.3 Eisenmangel bei Patienten mit Schlaganfall

Unseren Untersuchungen zufolge, hatten die Patienten sowohl im Akutstadium als auch im chronischen Stadium einen Eisenmangel. Während im Akutstadium knapp die Hälfte der Patienten vom Eisenmangel betroffen waren, erhöhte sich nach einem Jahr die Prävalenz des Eisenmangels

auf 77% der Patienten. Patienten mit Eisenmangel hatten eine Kraftminderung und einen schlechteren funktionellen Status im Vergleich zu nicht betroffenen Patienten. Im chronischen Stadium zeigten Patienten mit Eisenmangel keine Verbesserung der Muskelkraft mehr. Ähnliche Ergebnisse zeigte eine weitere Studie, die den Eisenmangel bei Patienten in der Frührehabilitation nach Schlaganfall untersuchte [136]. Diese Studie zeigte eine geringere funktionelle Kapazität unabhängig von Anwesenheit einer Anämie bei Patienten mit ID, während die Kombination mit Anämie sich additiv auf die eingeschränkte Funktionsfähigkeit auswirkte. Eine weitere Studie zeigte den Eisenmangel als unabhängigen Risikofaktor der schlechteren funktionellen Genesung bei geriatrischen Patienten [137].

Eine vor kurzem publizierte Studie berichtet, dass die Prävalenz von Eisenmangel bei der europäischen Bevölkerung über 70 Jahre bei 27% lag und sich auf 45% innerhalb von drei Beobachtungsjahren erhöhte [138]. In unserer Studie sahen wir viel höhere Werte im Akutstadium. Ob der Eisenmangel akut im Rahmen des Schlaganfalls aufgetreten ist oder bereits vor dem Schlaganfall vorhanden war, kann ohne zusätzliche Untersuchungen nicht gesagt werden. Klar ist aber, dass bereits ein Eisenmangel zum Zeitpunkt des Schlaganfalls prädiktiv für einen niedrigeren funktionellen Zustand ist.

Die pathophysiologischen Ursachen für einen Eisenmangel hat unsere Studie nicht evaluiert. Es häufen sich aber Hinweise für eine chronische Inflammation als Ursache, die durch die Hochregulierung vom Hepcidin bei chronischen Erkrankungen den Eisenmangel verursachen könnte [139,140]. Durch den hohen Hepcidin-Spiegel im Serum kommt es dabei zur Hemmung der intestinalen Eisenabsorption und zur intrazellulären Eisenblockade [141]. Ob ein ähnlicher pathophysiolgischer Mechanismus den Eisenmangel bei Patienten mit Schlaganfall verursacht, sollte in weiteren Studien evaluiert werden.

3.4 Vegetative Dysregulation nach Schlaganfall

Wir konnten die vegetativen Störungen, wie endotheliale Dysfunktion, verminderte HRV und schlafbezogenen Atemstörungen bei einer großen Anzahle der Patienten im Akutstadium, während der Frührehabilitation und im chronischen Stadium nach Schlaganfall beobachten. Wie erwartet, waren die vegetativen Störungen mit niedrigen physischen und funktionellem Status assoziiert. Die

reduzierte HRV war bei jedem 5. Patienten während der Frührehabilitation festzustellen und war unabhängig mit kumulativer funktioneller Behinderung assoziiert. Des Weiteren wurden die schlafbezogenen Atemstörungen bei 64% der Patienten im Akutstadium nachgewiesen, von denen nur noch 15% der Patienten nach einem Jahr nach Schlaganfall betroffen waren. Patienten mit normalisierter Schlafatmung zeigten auch eine normalisierte periphere Endothelfunktion.

3.5 Physischer Status

Sowohl die kachektischen Patienten als auch Patienten mit Eisenmangel hatten einen reduzierten physischen Status und niedrigere Muskelkraft im Vergleich zu nicht-kachektischen Patienten. Es konnte keine Verbesserung der Muskelkraft bei Patienten mit Eisenmangel nach einem Jahr festgestellt werden. Diese Ergebnisse sind ähnlich den Ergebnissen anderer Studien, die Patienten mit chronischen Erkrankungen und Kachexie [142,143] oder Eisenmangel [144,145] untersucht haben. Wie auch in der SICA-HF (Studies Investigating Comorbidities Aggravating Heart Failure) Studie [146], war in unsere Studie geringere Muskelkraft mit geringerer Magermasse assoziiert.
Zusätzlich zu physischen Status und Muskelkraft, haben wir einen erhöhten CAF22 Serumspiegel bei Patienten zu Beginn der Frührehabilitation nach Schlaganfall feststellen können [147]. Diese Erhöhung vom CAF22 war mit der reduzierten Muskelkraft und Magermasse assoziiert und sank am Ende der Rehabilitation nur bei Patienten, die ihre Magermasse vergrößert haben, ab. Unsere Ergebnisse stimmen mit den Ergebnissen der SICA-HF Studie überein, die eine Assoziation zwischen Agrin-Fragmenten, TotalCAF und CAF22, und verringerter Muskelmasse und Muskelkraft sowie körperlicher Leistung bei Patienten mit CHI nachgewiesen haben [88]. Unsere Ergebnisse gaben den ersten Hinweis, das CAF22 als Marker für die Diagnose der schlaganfallassoziierten Sarkopenie verwendet werden kann. Die weitere Testung des CAF22 als Marker des Muskelabbaus beim Schlaganfall sollte in größeren Patientenkohorten überprüft werden.

3.6 Ausblick

Als unsere longitudinalen Studien The Body Size in Stroke Study (BoSSS) und The Body Size in Stroke Study Rehabilitation (BoSSS-Reha) entworfen wurden, die das metabolische Profil in Assoziation mit

Gewebeschwund und funktionellem Outcome nach Schlaganfall untersuchen sollten, haben sowohl die Leitlinien der Europäischen Gesellschaft für Schlaganfall (European Stroke Organisation, ESO) als auch der Amerikanischen Gesellschaft für Kardiologie und Schlaganfall (American Heart and American Stroke Association, AHA/ASA) für sekundäre Schlaganfall Prophylaxe eine Gewichtsreduktion empfohlen [148,149]. Die intensive interdisziplinäre Forschung in den letzten Jahren der Schlaganfallassoziierten metabolischen Komorbiditäten hat gezeigt, dass das Übergewicht und Adipositas auf den Outcome einen positiven Effekt haben, während Gewichtsverlust und niedriges Ausgangsgewicht als prognostisch ungünstige Faktoren zu bewerten sind und mit schlechterem klinischen und niedrigeren funktionellen Status assoziiert sind. Diese Erkenntnisse führten dazu, dass der Nutzen einer Gewichtsreduktion zur Vorbeugung eines Schlaganfallrezidivs bei Patienten nach TIA oder ischämischem Schlaganfall in der aktuellen Leitlinie für Sekundärprophylaxe als ungewiss bewertet wird [150].

Die Prävalenz und prognostische Relevanz der schlaganfallassoziierten Kachexie als wesentliche metabolische Komorbidität und die Rolle der sämtlichen ursächlichen Faktoren wie Inflammation, reduzierte anabole Stimulation, verminderter Kalorienzufuhr, negative Proteinbilanz und Malabsorption sollten weiter in großen klinischen Studien untersucht werden. Unsere Untersuchungen hatten einen Pilotcharakter. Longitudinale klinische Studien an größeren Patientenkohorten sollten zeigen, ob unsere Hypothese des katabolen/anabolen Ungleichgewichtes in der Entstehung der schlaganfallassoziierten Kachexie bestätigt wird.

Bei Patienten mit chronischer Herzinsuffizienz ist Eisenmangel prognostisch relevant. Die FAIR-HF [151] und CONFIRM-HF Studie [152] sowie andere klinische Studien [141] zeigten einen positiven Effekt auf Ausdauer, Symptome der Herzinsuffizienz, Lebensqualität und HF-Hospitalisierungen nach intravenösen Gabe von Eisen [153]. Die aktuelle ESC Leitlinie für Herzinsuffizienz 2021 empfiehlt die intravenöse Substitution von Eisen(III)-Carboxymaltose bei Patienten mit Eisenmangel und linksventrikulärer Auswurffunktion LVEF <45% bzw. <50% [154].

Bis dato sind es zwei Beobachtungsstudien, die den Eisenmangel und seine negative Auswirkung auf klinische und funktionelle Prognose nach Schlaganfall untersucht haben. Der Beweis eines Nutzens von intravenöser Eisensubstitution auf den Outcome nach Schlaganfall steht noch aus. Ob eine intravenöse Substitution von Eisen(III)-Carboxymaltose als mögliche zukünftige therapeutische Option beim Schlaganfall in Frage kommt, sollte in Interventionsstudien evaluiert werden.

4 Zusammenfassung

Ein Schlaganfall geht häufig mit einem katabolen/anabolen Ungleichgewicht, vegetativer Dysregulation und systemischer Inflammation einher, welche ihre Auswirkung auf funktionelle und körperliche Leistungsfähigkeit des Patienten haben und den Krankheitsverlauf sowie den Rehabilitationserfolg negativ beeinflussen können. Ziel dieser Arbeit war es die metabolischen Aspekte der schlaganfallassoziierten Komorbiditäten systematisch zu charakterisieren.

Wir konnten zeigen, dass die metabolische Dysregulation nach Schlaganfall alle Stadien der Erkrankung (Akutstadium, Subakutstadium und chronisches Stadium) beeinflussen kann. Diese Dysregulation geht mit einem Eisenmangel, Kachexie, Verlust von Muskelkraft, atembezogenen Schlafstörungen, Veränderungen der Herzratenvariabilität und endothelialer Dysfunktion einher. Diese metabolischen Komorbiditäten haben einen zeitabhängigen dynamischen Charakter. Während bei Kachexie die Gewichtsveränderungen innerhalb eines Zeitraumes von 6-12 Monate beurteilt werden, sind die Veränderungen der Skelettmuskulatur (Muskelkraft und Muskelmasse) bereits innerhalb von einigen Tagen bzw. Wochen nach Schlaganfall nachweisbar. Wir konnten zeigen, dass die schlafbezogenen Atemstörungen und periphere endotheliale Dysfunktion in einem Zusammenhang zueinanderstehen und eine Besserung der einen Störung zu einer Besserung der anderen führt. Diese Tatsache kann auf eine spontane Wiederherstellung der funktionellen Integrität beeinträchtigter vegetativer Zentren hinweisen. Die Prävalenz des Eisenmangels erhöhte sich dramatisch nach einem Jahr nach Indexschlaganfall. Als therapeutische Konsequenz wären z.B. die engmaschigere Kontrolle der Eisenparameter sowie eine Substitutionstherapie sinnvoll.

Unsere Arbeiten haben erste Ansatzpunkte geliefert, die in longitudinalen Studien an größeren Patientenkohorten weiterentwickelt werden müssen, um den Weg zu klinischen Therapieoptionen bei Patienten mit metabolischen Komorbiditäten zu unterstützen.

5 Anhang

Tabelle A1. Barthel Index [19].

Funktion (Punkte)
Essen: •Unfähig allein zu essen (0) • Braucht etwas Hilfe, z. B. Brot schmieren (5) • Selbständig, braucht keine Hilfe (10)
Baden: • Abhängig von fremder Hilfe (0) • Selbständig, benötigt keine Hilfe (5)
Körperpflege: • Abhängig von fremder Hilfe (0) • Selbständig, benötigt keine Hilfe (5)
An- und Auskleiden: • Unfähig, sich allein an- und auszuziehen (0) • Braucht etwas Hilfe, kann aber 50% alleine durchführen (5) • Selbständig, benötigt keine Hilfe (10)
Stuhlkontrolle: • Inkontinent (0) • Gelegentlich inkontinent (max. 1/ Woche) (5) • Ständig inkontinent (10)
Urinkontrolle: • Inkontinent (0) • Gelegentlich inkontinent (max. 1/ Tag) (5) • Ständig inkontinent (10)
Toilettenbenutzung: • Abhängig von fremder Hilfe (0) • Benötigt Hilfe wegen fehlenden Gleichgewichts, oder beim ausziehen (5) • Selbständig, benötigt keine Hilfe (10)
Bett- bzw. Stuhltransfer: • Abhängig von fremder Hilfe, fehlende Sitzbalance (0) • Erhebliche physische Hilfe beim Transfer erforderlich, Sitzen selbständig (5) • Geringe physische bzw. verbale Hilfe oder Beaufsichtigung erforderlich (10) • Selbständig, benötigt keine Hilfe (15)
Mobilität: • Immobil bzw. Strecke > 50 m (0) • Unabhängig mit Rollstuhl, incl. Ecken, Strecke > 50 m (5) • Unterstütztes Gehen möglich, Strecke > 50 m (10) • Selbständiges Gehen möglich (Hilfsmittel erlaubt), Strecke > 50 m (15)
Treppensteigen: • Unfähig, alleine Treppen zu steigen (0) • Benötigt Hilfe oder Überwachung beim Treppensteigen (5) • Selbständiges Treppensteigen möglich (10)

Tabelle 1B. Rivermead Motor Assessment Scale [20].

Anweisungen Dem Patienten werden die folgenden 15 Fragen gestellt (Frage 5 wird beobachtet). Für jede `JA' Antwort wird ein Punkt vergeben. Beachten Sie, dass die meisten Fragen die Unabhängigkeit von einer Hilfsperson erfordern, die Art der Durchführung ist aber sonst unerheblich.
1 Umdrehen im Bett Drehen Sie sich ohne Hilfe von der Rückenlage in die Seitenlage?
2 Vom Liegen zum Sitzen Setzen Sie sich vom Liegen ohne Hilfe an die Bettkante?
3 Gleichgewicht im Sitzen Sitzen Sie 10 Sekunden am Bettrand, ohne sich anzuhalten?
4 Vom Sitzen zum Stehen Stehen Sie von einem Sessel in weniger als 15 Sekunden auf und stehen Sie 15 Sekunden lang (mit Anhalten und mit einem Hilfsmittel, wenn nötig)?
5 Stehen ohne Unterstützung Beobachten Sie 10 Sekunden lang das Stehen ohne Hilfsmittel oder Unterstützung
6 Überwechseln Schaffen Sie es, ohne Hilfe, zum Beispiel vom Bett auf einen Sessel und zurück überzuwechseln?
7 Gehen in der Wohnung, wenn nötig mit Hilfsmittel Gehen Sie in der Wohnung 10 Meter mit einem Hilfsmittel, oder mit Anhalten an Möbelstücken, jedoch ohne Aufsicht?
8 Stiegensteigen Sind sie im Stande ein Stockwerk ohne Hilfe zu bewältigen?
9 Gehen im Freien auf ebenem Untergrund Gehen sie draußen am Gehsteig ohne Hilfe?
10 Gehen in Haus/Wohnung Gehen Sie drinnen 10 Meter ohne Aufsicht, ohne Stock oder Schiene und ohne Hilfsmittel und ohne sich an Möbeln anzuhalten?
11 Etwas vom Fußboden aufheben Wenn Ihnen etwas zu Boden fällt, schaffen Sie es 5 Meter zu gehen, den Gegenstand aufzuheben und wieder zurück zu gehen?
12 Gehen im Freien auf unebenem Untergrund Gehen Sie auf unebenem Untergrund (Gras, Schotter, Erde, Schnee, Eis) ohne Hilfe?
13 Baden Steigen Sie ohne Aufsicht in die Badewanne/Dusche ein und aus und waschen Sie sich selbständig?
14 Vier Stufen hinauf und hinunter Schaffen Sie es, ohne Unterstützung und ohne sich am Geländer anzuhalten, vier Stufen hinauf und hinunter zu steigen?
15 Laufen Laufen Sie10 Meter in vier Sekunden ohne zu Hinken (schnelles Gehen ohne Hinken ist ebenfalls erlaubt)?

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Erklärung

§ 4 Abs. 3 (k) der HabOMed der Charité

Hiermit erkläre ich, dass

- weder früher noch gleichzeitig ein Habilitationsverfahren durchgeführt oder angemeldet wurde,

- die vorgelegte Habilitationsschrift ohne fremde Hilfe verfasst, die beschriebenen Ergebnisse selbst gewonnen sowie die verwendeten Hilfsmittel, die Zusammenarbeit mit anderen Wissenschaftlern/Wissenschaftlerinnen und mit technischen Hilfskräften sowie die verwendete Literatur vollständig in der Habilitationsschrift angegeben wurden,

- mir die geltende Habilitationsordnung bekannt ist.

Ich erkläre ferner, dass mir die Satzung der Charité – Universitätsmedizin Berlin zur Sicherung Guter Wissenschaftlicher Praxis bekannt ist und ich mich zur Einhaltung dieser Satzung verpflichte.

11.10.2022

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