AUS DEM LEHRSTUHL FÜR NEUROLOGIE

PROF. DR. MED. ULRICH BOGDAHN

DER FAKULTÄT FÜR MEDIZIN

DER UNIVERSITÄT REGENSBURG

TRANSKRANIELLER KONTRASTMITTELGESTÜTZTER ULTRASCHALL ZUR DARSTELLUNG DER HIRNVERSORGENDEN GEFÄßE BEI SCHLAGANFALLPATIENTEN IM NOTARZTDIENST

Inaugural – Dissertation
zur Erlangung des Doktorgrades
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Zusammenfassung

1. Fragestellung und Hintergrund

Epidemiologie

Der ischämische Schlaganfall ist weltweit die dritthäufigste Todesursache und die häufigste Ursache für Frühinvalidität in den Industrienationen (Rothwell et al. 2005; Rosamond et al. 2008). Allein in Deutschland erleiden jedes Jahr ca. 260 000 Menschen einen Schlaganfall, bei dem ca. 1,9 Millionen Gehirnzellen pro Minute irreversibel geschädigt werden. Eine effektive Schlaganfalltherapie sollte schnellstmöglich auf einer spezialisierten Stroke Unit eingeleitet werden, getreu dem Motto „Time is Brain“ (Saver 2005). Dazu müssen Schlaganfallpatienten durch Angehörige, Notarzt und Rettungsdienst schnell und sicher identifiziert und in eine Stroke Unit gebracht werden.

Das Risiko, einen Schlaganfall zu erleiden, steigt mit zunehmendem Alter deutlich an (Heuschmann et al. 2009). Bedingt durch die epidemiologische Entwicklung, mit einer deutlichen Überalterung der Bevölkerung, ist von einem massiven Zuwachs an Schlaganfallpatienten auszugehen. Experten rechnen bis zum Jahr 2050 mit einer Steigerung der Gesamtzahl der Schlaganfallpatienten von mehr als 50% (Foerch et al. 2008). Aber nicht nur die primären Auswirkungen des Schlaganfalles, wie bleibende Behinderungen, beeinträchtigen die Patienten. Schlaganfälle sind auch die häufigste Ursache von Epilepsien im höheren Lebensalter, die zweithäufigste Ursache für die Entwicklung einer Demenz und eine häufige Ursache für Depressionen (Foerch et al. 2008; O'Brien et al. 2003). Zusammengefasst sind die medizinischen und sozioökonomischen Folgen des Schlaganfalls eine massive Herausforderung für die Gesellschaft.

Ätiologie

Der Schlaganfall geht klinisch mit akuten neurologischen Ausfallerscheinungen wie Lähmungen, Sensibilitäts- und Sprachstörungen, Bewusstlosigkeit oder Schwindel einher, für die es verschiedene Ursachen geben kann. Der häufigste Schlaganfalltyp ist ein Infarkt des Hirngewebes (Ischämie, ca. 80% aller Fälle) durch einen akuten Verschluss einer hirnversorgenden Arterie. Neben einem solchen akuten Gefäßverschluss kann eine Gehirnblutung (10%) ebenfalls Schlaganfallsymptome verursachen. Zudem kann das Erscheinungsbild eines Schlaganfalls auch bei anderen Erkrankungen, sogenannten „stroke mimics", auftreten. Dies sind u.a. epileptische Anfälle, Migräne, Infektionserkrankungen, Stoffwechselstörungen oder psychogene Anfälle. Da die neurologischen Symptome des Schlaganfalls bei einem Hirninfarkt und einer Hirnblutung durch Anamnese und klinische Untersuchung kaum unterschieden werden können, ist eine möglichst frühe spezifische Schlaganfalldiagnostik durch Computer- oder Kernspintomographie erforderlich.

Einen Eckpfeiler der ischämischen Schlaganfalltherapie bildet die medikamentöse Wiedereröffnung des Gefäßverschlusses, die Thrombolyse mittels „rekombinantem Gewebeplasminogenaktivator" (engl. rt-PA). Zugelassen ist die Therapie innerhalb von 4,5 Stunden nach Symptombeginn, zuletzt belegt durch die ECASS 3 Studie (European Cooperative Acute Stroke Study) (Hacke et al. 2008). Die Mehrheit der Patienten profitiert allerdings nicht von dieser Therapieoption, da weniger als 25% der Patienten innerhalb von 2 Stunden nach Einsetzen der Symptome und nur 36% innerhalb von 3 Stunden (Bayerische Gesellschaft für Qualitätskontrolle, Bericht 2012) auf eine Stroke-Unit aufgenommen werden (Albers und Olivot 2007; Lichtman et al. 2009). Signifikante präklinische Verzögerungen sind einer der Hauptgründe, warum Patienten keine wirksame Behandlung erhalten (Evenson et al. 2009). Neuere Analysen aus früheren Studien zeigen eine mediane präklinische Verzögerung zwischen 35 Minuten und 71 Minuten (Puolakka et al. 2010; Teuschl und Brainin 2010). Zudem sinkt die Chance auf eine vollständige Genesung innerhalb des 4,5 Stunden Zeitfensters in Abhängigkeit der Zeit signifikant (Abbildung 1). Wird die Therapie innerhalb von 90 Minuten begonnen erholt sich einer von vier behandelten Patienten. Zwischen 90 Minuten und 3 Stunden bedarf es schon neun behandelter Patienten, um eine vollständige Heilung durch die Therapie zu erreichen.

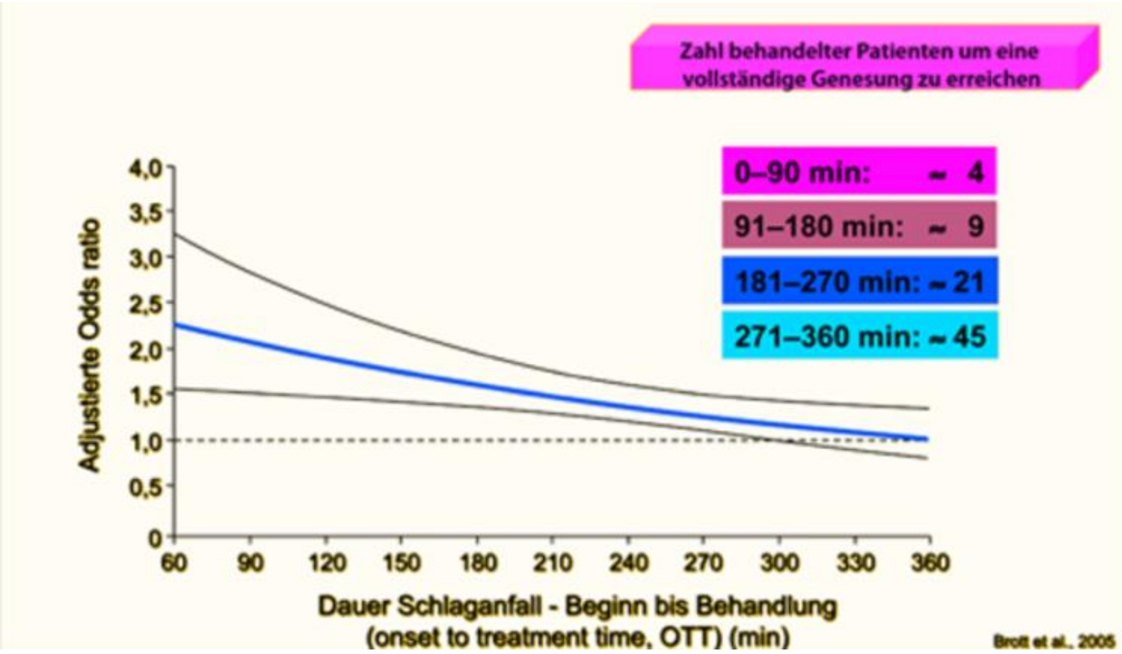


Abbildung 1

Transkranielle farbkodierte Duplexsonographie

Die transkranielle Ultraschalldiagnostik ist eine schnelle und nicht-invasive Methode zur Beurteilung der Hirnarterien beim akuten Schlaganfall und ein Routinewerkzeug auf den Stroke-Units. Insbesondere in Kombination mit Kontrastmittel ist die diagnostische Wertigkeit vergleichbar mit der Computertomographischen-Angiographie (CTA) und der Magnetresonanz-Angiographie (MRA) bei Gefäßpathologien vor allem im Mediastromgebiet (MCA) (Boddu et al. 2011; Brunser et al. 2009; Tsivgoulis et al. 2007).

Laut der Studie „Neurosonology in acute stroke patients“ liefert die neurosonographische Diagnostik sogar einen unabhängigen Vorhersagewert für das Outcome der Schlaganfallpatienten (Allendoerfer et al. 2006).

Studienverlauf

In einer Pilotstudie wurde die grundsätzliche Realisierbarkeit des transkraniellen Ultraschalles mit Hilfe eines tragbaren Ultraschallgerätes innerhalb von 5 bis 10 Minuten bestätigt (Hölscher et al. 2008). In der jetzt durchgeführten zweiten Phase des Projektes sollte die Sensitivität und Spezifität der Ultraschalluntersuchungen von proximalen MCA- Verschlüssen durch den Vergleich mit Ergebnissen der radiologischen Gefäßdarstellung (CCT, CTA, MRA) sowie den Enddiagnosen untersucht werden. Zur Steigerung der Untersuchungsqualität konnte ein Ultraschall-Kontrastmittel verwendet werden. Weitere wichtige Fragestellungen waren auch die für die Ultraschall-Untersuchung benötigten Zeiten sowie die Zeiten für An- und Abfahrt des Rettungsteams.

Ein Endziel dieses Gemeinschaftsprojektes zwischen der Universität Regensburg und dem „Brain Ultrasound Research Laboratory“ der Universität Sand Diego, USA, ist die effektive Nutzung der Transportzeit für neuroprotektive Maßnahmen sowie die Etablierung der prähospitalen „Sonothrombolyse“.

2. Material und Methoden

Studiendesign

Die Studie wurde zwischen Mai 2010 und Januar 2011 in einem Radius von 35 km um das Bezirksklinikum Regensburg durchgeführt (Abbildung 2). Der Landkreis Regensburg versorgt mit seinen zwei Stroke-Unit-Stützpunkten eine Bevölkerung von ca. 150 000 Personen in Ostbayern.

Patienten, welche sich im Einzugsbereich der Leitstelle Regensburg mit Schlaganfall verdächtigen Symptomen über den Notruf „112“ meldeten, wurden in die Studie eingeschlossen. Die Leitstelle alarmierte neben dem Notarzt und der Rettungsdienstbesatzung einen im transkraniellen Ultraschall erfahrenen Neurologen welcher im Rendezvous-System (Abbildung 3) bei den Patienten eintraf und neben der rettungsdienstlichen Notfallversorgung zusätzlich eine neurologische Untersuchung sowie einen transkraniellen Ultraschall beider ACM durchführte.

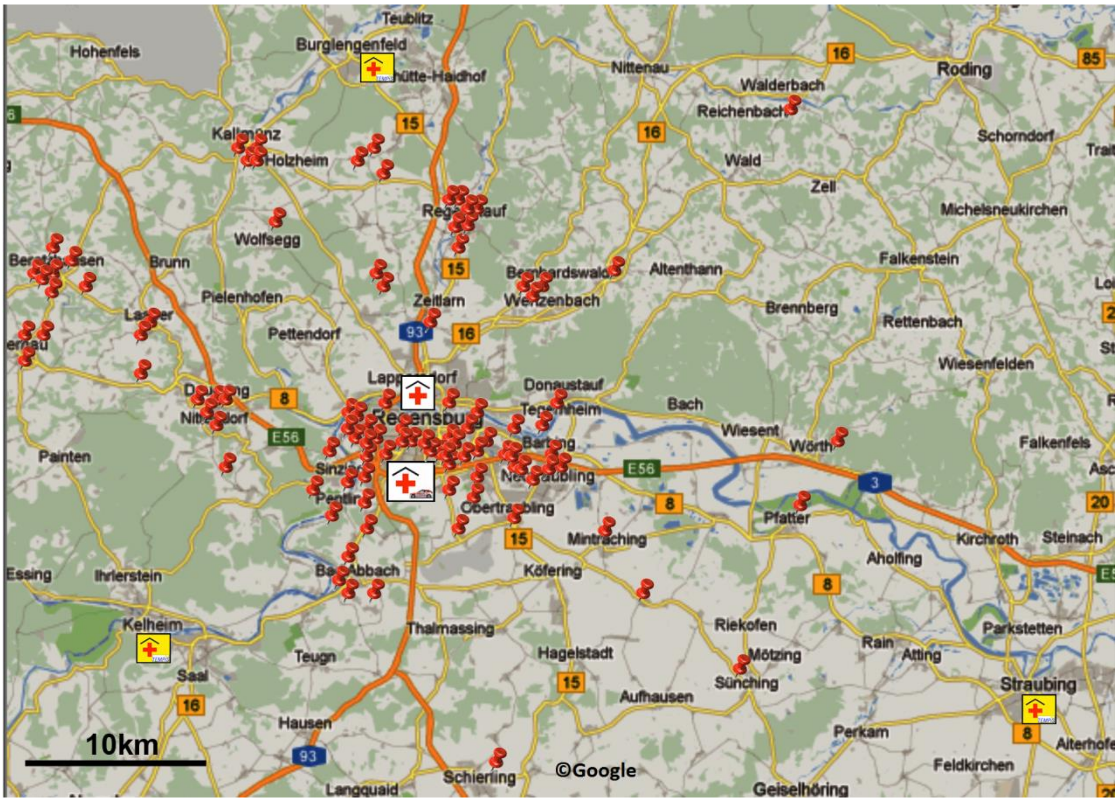


Abbildung 2

Der Ultraschall wurde entweder vor Ort oder im fahrenden Rettungswagen durchgeführt. Bei erschwerten Schallbedingungen oder zur Erhöhung der diagnostischen Wertigkeit wurde ein Ultraschallkontrastmittel eingesetzt. Mithilfe eines Fragebogens wurden die Zeitintervalle der Anfahrt, Untersuchungszeit vor Ort, Rückfahrt sowie die Verdachtsdiagnose und die Beurteilung der Ultraschall-Untersuchung dokumentiert. Patienten welche nach gemeinsamer Einschätzung des Neurologen sowie des Notarztes keinerlei neurologische Symptome zeigten wurden nicht mittels Ultraschall untersucht und nicht in die Studie eingeschlossen.

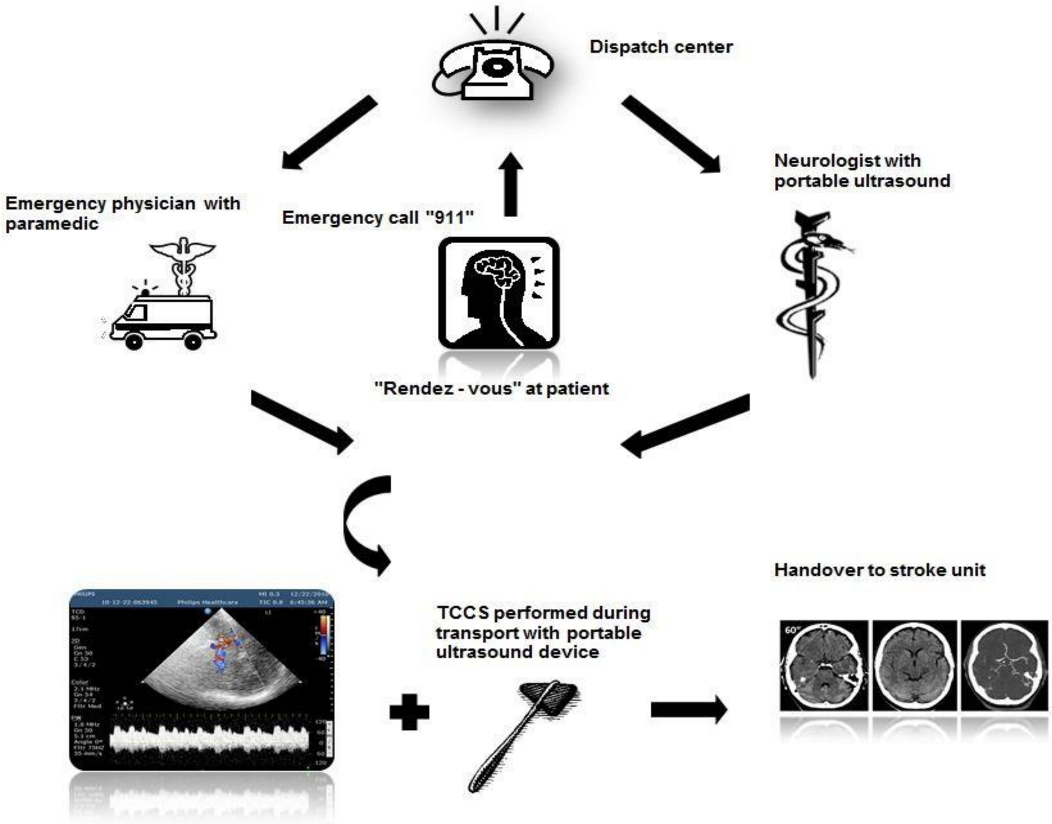


Abbildung 3

Patienten mit dem Verdacht auf einen Schlaganfall wurden zur weiteren Behandlung der nächstgelegenen Stroke-Unit übergeben. Die unter stationären Bedingungen durchgeführte Diagnostik (Ultraschall, CT, CT-Angiographie, MRT, MRT-Angiographie) sowie die Enddiagnosen aus den Entlassbriefen wurden mit den präklinisch erfassten Daten verglichen und daraus die Sensitivität und Spezifität der Ultraschalluntersuchung sowie die Anzahl der präklinisch richtig gestellten Verdachtsdiagnosen berechnet.

Ultraschallgeräte und Datenerfassung

In der Studie wurden zwei mit 2MHz Ultraschallköpfen bestückte tragbare Ultraschallgeräte (SonoSite Micromaxx®, Philipps CX50®) von den durch die Deutsche Gesellschaft für Ultraschallmedizin (DEGUM) zertifizierten Neurologen eingesetzt. Als Kontrastmittel konnten i.v. 0,5 – 2ml sogenannter „Microbubbles“ der Firma SonoVue®

eingesetzt werden, um bei schlechtem Schallfenster die diagnostische Aussagekraft der Untersuchung zu steigern. Die Untersuchung erfolgte beidseits über das temporale Knochenfenster, dem konventionellen Zugang für transkranielle Ultraschalluntersuchungen, um die hirnversorgenden Gefäße bildlich darzustellen.

Das Untersuchungsprotokoll sah die Darstellung und Flussmessung beider proximaler Anteile der ACM ohne Winkelkorrektur bei der Doppleruntersuchung vor. Im Falle einer pathologischen Flussveränderung, im Sinne eines Gefäßverschlusses oder einer hämodynamisch relevanten Stenose, wurde diese bildlich sowie dopplersonographisch dokumentiert. Ein proximaler Gefäßverschluss (Karotis T, M-1 Segment) wurde nach den Kriterien der Konsensus- Empfehlung von 2009 diagnostiziert (Nedelmann et al. 2009). Ein distaler Verschluss der ACM wurde nach den von Zanette et. al publizierten Kriterien bewertet (Zanette et al. 1989). Der Untersucher konnte ggf. das Protokoll erweitern und auch die Arteriea cerebri anteriores (ACA) untersuchen um so z.B. anhand des „crossfilling“ Phänomens indirekt auf einen Verschluss der ACI schließen zu können. Ein Verschluss der ACI wurde diagnostiziert, wenn in der ipsilateralen ACA ein retrograder Fluss („crossfilling“) gemessen wurde, was nach den ESCT-Kriterien auf eine über 80%ige Stenose oder Verschluss der ACI hinweist (Arning et al. 2010). Diese Verdachtsdiagnosen wurden mit ausgewertet, waren aber nicht Teil der primären Fragestellung.

3. Ergebnisse

Insgesamt wurde das Rettungsteam in 232 Fällen mit Verdacht auf Schlaganfall alarmiert, wovon nur 102 Patienten mit neurologischen Symptomen und vollständigem Datensatz in die Studie eingeschlossen werden konnten. Davon erhielten 73 Patienten die Enddiagnose „Schlaganfall“ (ischämisch, hämorrhagisch, transiente ischämische

Attacke). Als sogenannte „stroke mimics“ wurden 29 Patienten klassifiziert. Die häufigsten Enddiagnosen der sogenannten “stroke mimics” waren epileptische Anfälle, Hirntumoren, Exsikkosen, Hypoglykämien oder kardiale Synkopen.

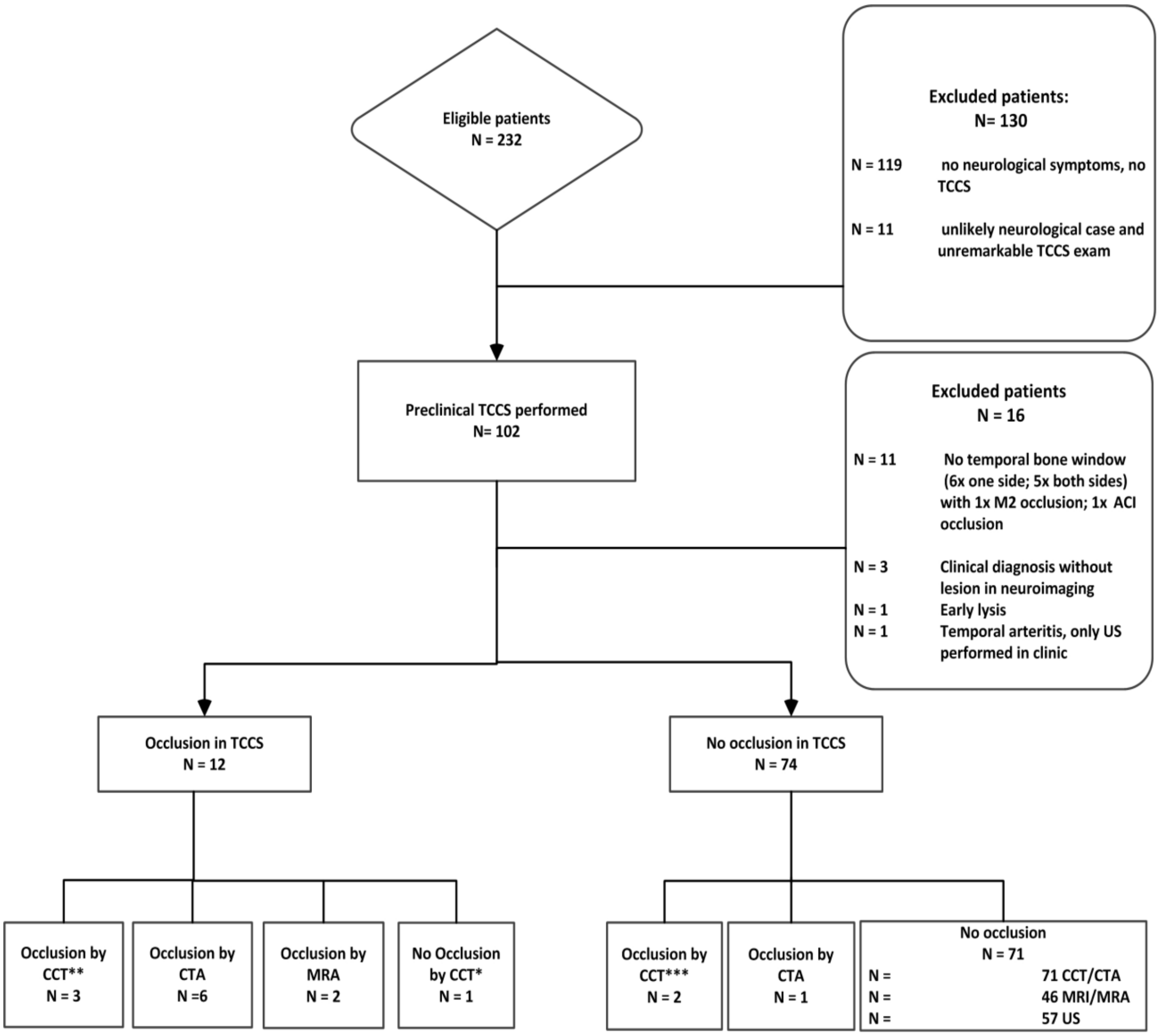
Das Durchschnittsalter der Patienten lag bei 80,6 Jahren (± 13,52), wobei 56 % der Patienten weiblich waren. Mehr als die Hälfte der Untersuchungen wurde bei den Patienten zu Hause (50%), in einer Praxis (4%) beziehungsweise im Altenheim (2%) durchgeführt. Während des Transportes im Rettungswagen wurden 43% der Patienten mittels Ultraschall untersucht. Das Ultraschallkontrasmittel wurde in 40% der Untersuchungen verwendet. Trotzdem mussten erwartungsgemäß 11% der Patienten von der Studie ausgeschlossen werden, da sie entweder einseitig oder beidseits kein ausreichendes Schallfenster boten. Fünf weitere Patienten wurden ausgeschlossen. Ein Patient mit einer mutmaßlich spontanen Thrombolyse während des Transportes. Ein Patient mit einer Arteriitis temporalis sowie drei Patienten mit unauffälligen neuroradiologischen Befunden aber der Enddiagnose „Schlaganfall“ im Entlassbrief. Das Flussdiagramm veranschaulicht den Diagnosepfad (Abbildung 4).

Unter den zerebralen Ischämien fanden sich 10 Verschlüsse der ACM sowie 4 Stenosen der ACI. Innerhalb dieser Gruppe wurden präklinisch 11 der 14 Verschlüsse richtig erkannt und radiologisch durch CTA oder MRA bestätigt. Ein Verschluss der ACM und 2 ACI-Stenosen sowie eine atypische Blutung wurden fehldiagnostiziert. Die aus diesen Ergebnissen berechnete Sensitivität für die ultraschallgestützte Darstellung der Stenosen insgesamt (ACM und ACI) beträgt 78%, mit einer Spezifität von 98%. Für die mittels Ultraschall und neurologischer Untersuchung richtig gestellte Verdachtsdiagnose (Schlaganfall Ja/Nein) wurden eine Sensitivität von 94% und eine Spezifität von 48% errechnet.

Die Untersuchungszeit für den transkraniellen Ultraschall betrug im Durchschnitt 5 Minuten und 36 Sekunden (SD ± 2 min. und 12 sec.) und verlängerte die Einsatzzeit vom

Eintreffen beim Patienten bis zur Übergabe an die weiterbehandelnde Klinik von durchschnittlich 53 Minuten nicht. Durchschnittlich 11 Minuten benötigte das Rettungsteam vom Einsatzalarm bis zur Ankunft beim Patienten.

Während der Studiendauer erhielten 9 von 50 Patienten (18 %) eine i.v. Thrombolyse und ein Patient wurde mechanisch thrombektomiert. Nur 5% der neurologischen Symptome in der Studie wurden durch eine Blutung verursacht.



* ICH
** demarkation of large ischemia in cCT in 1 patient, 2 „dense artery" signs
*** demarkation of large ischemia in cCT in 2 patients

Diagnostic accuracy:

Artery	Se (95%CI)	Sp (95%CI)	PPW (95%CI)	NPW (95%CI)
M_1/ICA	78% (49–95)	98% (92–99)	91% (61–99)	95% (88–99)
M_1	90% (55–99)	98% (92–99)	90% (55–99)	98% (92–99)

Abbildung 4

4. Diskussion:

Prähospitale Schlaganfalldiagnostik

Mehr als die Hälfte der von der Leitstelle mit dem Meldebild „ Schlaganfall“ angemeldeten Patienten konnten durch die klinische Untersuchung und „neurologische Blickdiagnose“ als „kein Schlaganfall“ identifiziert werden.

Der hohe Anteil der Patienten (56%, 130 von 232 Patienten), die von der Studie ausgeschlossen wurden, da sie keine neurologischen Symptome aufwiesen, zeigt die Schwierigkeit für die Leitstellenmitarbeiter am Telefon anhand von Schlagworten und Scoring-Systemen zwischen Schlaganfall und Nicht-Schlaganfall-Symptomen zu unterscheiden. Bei den mit Ultraschall untersuchten Patienten mit neurologischen Symptomen wurde die präklinisch gestellte Verdachtsdiagnose „Schlaganfall Ja/Nein“ mit einer Sensitivität von 94% und einer Spezifität von 48% identifiziert. Diesem scheinbar enttäuschenden Ergebnis der Spezifität für die Verdachtsdiagnose steht die für die Studie entscheidende hohe diagnostische Sensitivität und Spezifität des transkraniellen Ultraschalls bei Patienten mit M-1-ACM Verschlüssen (90% Sensitivität und Spezifität von 98%) oder kombinierten Pathologien im vorderen Kreislauf (78% Sensitivität und Spezifität 98%), für die die Studie nicht ausgelegt war, gegenüber.

Diagnostische Wertigkeit der neurovaskulären Bildgebung

Der Beginn einer spezifischen Therapie des ischämischen Schlaganfalles erfordert zunächst den Ausschluss einer Blutung. Hierfür ist die Empfindlichkeit des CCT unbestritten (Barber et al. 2000). Vergleicht man die bildgebenden Modalitäten untereinander zeigt das MRT mit einer diffusionsgewichteten Sequenz (DWI) am frühsten die höchste Sensitivität und Spezifität. Zusätzlich hat die DWI einen sehr guten Vorhersagewert für die die potentiell zu rettende „Penumbra“ (Fiebach 2002; Barlinn und Alexandrov 2011). Im klinischen Alltag erhalten allerdings nur ca. 14% der Patienten in einer Notaufnahme ein MRT und nur 29 % der Patienten innerhalb der ersten 12 Stunden (Burke et al. 2012). Ein Notfall-MRT wird meist nur an universitären Zentren vorgehalten. Der Betrieb ist häufig auf Werktage und normale Arbeitszeiten (8-18 Uhr) beschränkt und bringt aus logistischen Gründen ein großes zeitliches Verzögerungspotential mit sich, wobei bei der Therapieentscheidung „time is brain" als höchste Prämisse gelten sollte.

Eine gute Aussagekraft bezüglich der „Penumbra", z.B. bei unklarem Lyse-Zeitfenster, bietet auch die CT-Perfusion (Muir et al. 2006;). Allerdings beherrschen nur wenige Kliniken die Durchführung und Auswertung der sehr strahlenintensiven Untersuchung. Die kraniale Computertomographie (CCT) zeigt eine nur mäßige Empfindlichkeit für die Detektion von frühen Infarktzeichen. Je nach Studie und abhängig davon zu welchem Zeitpunkt die CT-Untersuchung durchgeführt wurde werden frühe Infarktzeichen im CT mit einer durchschnittlich Sensitivität von 66% (20% -87 %) bei einer Spezifität von 87% (56 % -100 %) erkannt (Wardlaw und Mielke 2005; Kummer et al. 2001; Chalela et al. 2007). Man kann jedoch argumentieren, dass für die Therapie des ischämischen Schlaganfalles innerhalb der ersten 4,5 Stunden mit rt-PA allein der Ausschluss eine Blutung mittels CCT ausreichend ist. Auf der anderen Seite erreicht rt-PA nur eine niedrige Rekanalisationsrate insbesondere bei proximalen Gefäßverschlüssen (distale ACI 4,4%; M1 -ACM (32,3 %), M2 -ACM (30,8 %)) (Bhatia et al. 2010), die nur in der Kombination mit einem interventionell-radiologischen Ansatz („bridging") deutlich verbessert werden kann (Rahme et al. 2013; Costalat et al. 2011). Auch wenn aktuelle Studien den langfristigen Nutzen eines interventionellen Ansatzes im Allgemeinen in Frage stellen, zeigen sie in den Subgruppenanalysen (M1-ACM, Karotis-T-Verschlüsse), welche im Fokus dieser Studie standen, deutliche Vorteile für das Outcome der Patienten (Broderick et al. 2013). Des Weiteren betonen sie die Notwendigkeit einer frühen Diagnostik gerade für die endovaskuläre Therapie. Bereits bei einer Verzögerung der Therapie von nur einer Stunde ist der Vorteil der höheren Rekanalisationsrate mit verbessertem Outcome im langfristigen Verlauf nicht mehr vorhanden, da bereits zu viel Gewebe zerstört wurde (Ciccone et al. 2013).

In vielen Studien hat der auf Station durchgeführte transkranielle Ultraschall eine hohe Übereinstimmung mit den Ergebnissen der CTA bewiesen und sich auch als verlässliche Diagnostik für die Entscheidung zur interventionellen Behandlung erwiesen (Tsivgoulis et al. 2007; Allendoerfer et al. 2006; Mikulik et al. 2006).

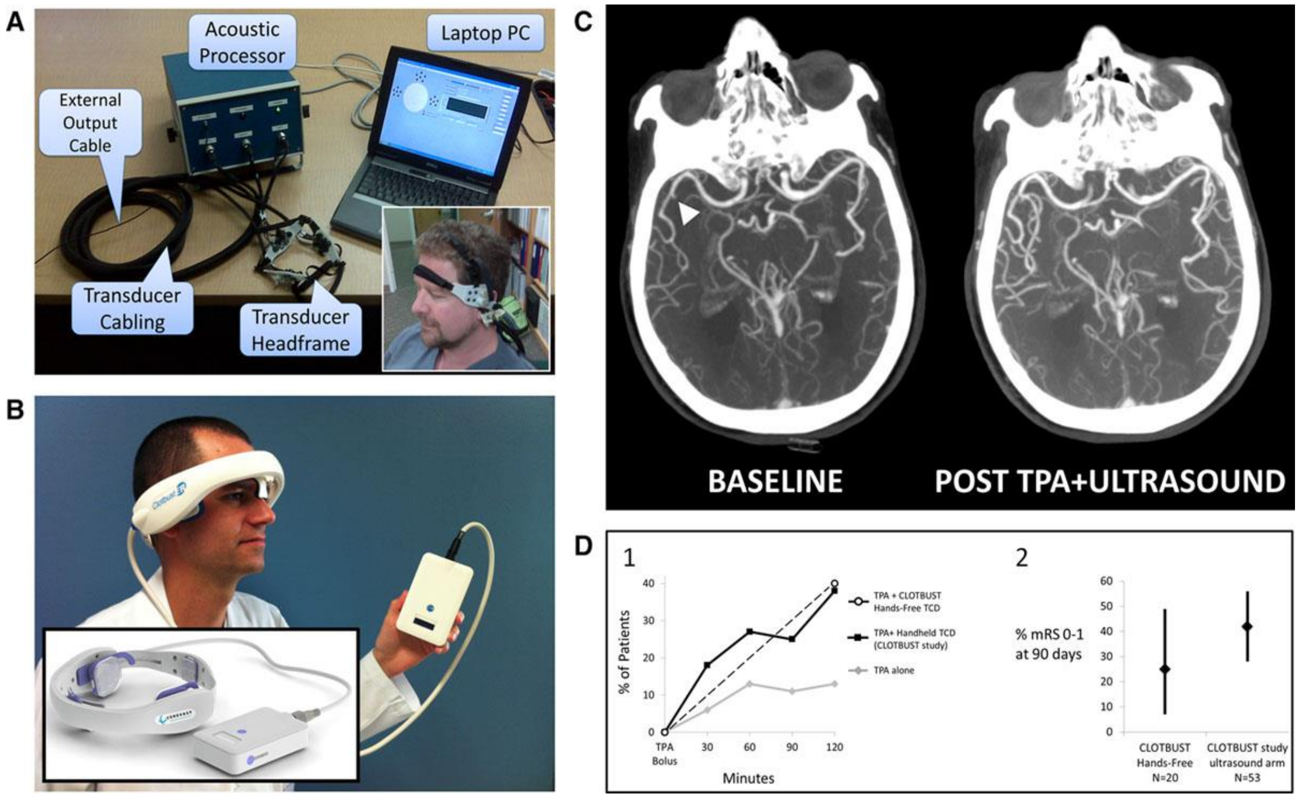


Abbildung 5

In dieser unter erschwerten prähospitalen Bedingungen durchgeführten Studie erreichte die diagnostische Wertigkeit der Ultraschalluntersuchung vergleichbare Werte wie die unter kontrollierten Bedingungen, innerhalb eines Krankenhauses, durchgeführten Studien (Brunser et al. 2009). Die Vielfalt der Positionen in denen der Patient prähospital untersucht werden muss, erfordert allerdings eine umfangreiche Erfahrung auf dem Gebiet des transkraniellen Ultraschalls, sodass die von uns erzielten Ergebnisse nur durch sehr erfahrene Untersucher erzielt werden können. In Zukunft könnten hier verschiedene Hilfsmittel (Kopfhalterungen etc.) den Einsatz des transkraniellen Ultraschalles erleichtern (Abbildung 5) (Barreto et al. 2013).

Präklinische Schlaganfall-Projekte in Deutschland

Momentan sind in Deutschland eine Vielzahl von präklinischen Schlaganfall-Projekten im Gange. Beispiele dafür sind das „Stroke-Angel-Projekt“ (V. Ziegler (1) 2011) (Ebinger et al. 2012), die „Mobile Stroke Unit“ (MSU) (Walter et al. 2012), Aster (www.aster-magdeburg.de) und Med-on-@ ix (Skorning et al. 2009). All diese Projekte unterscheiden sich jedoch in ihrer Konzeption, personellen Ausstattung und Kosten.

Das aktuelle MSU-Konzept zielt darauf ab, leitliniengerechte Schlaganfallbehandlung an den Einsatzort zu bringen (Walter et al. 2012). Hierfür wurde ein Krankenwagen speziell umgebaut und mit einem fahrbaren CT, einem „point-of-care“ Labor sowie einer telemedizinischen Anbindung ausgestattet. Damit konnte in einer randomisierten und kontrollierten Studie die Zeit vom Alarm der Leitstelle bis zur Therapieentscheidung deutlich von 76 min in der Kontrollgruppe auf 35 min in der MSU–Gruppe reduziert werden. Allerdings waren die Entfernungen zum Krankenhaus zwischen der Kontrollgruppe und der MSU-Gruppe unterschiedlich (6km (4-10km) gegenüber 8km (6-15km) in der Kontrollgruppe) und viel kürzer als in dieser Studie (10km (2-41km)). Im Vergleich zur dieser Studie, in der aufgrund eines schlechten Schallfenster in 10% der Fälle keine Untersuchung durchgeführt werden konnte, kam es in der MSU-Studie in 18% der angefahrenen Patienten zu einem technischen Defekt des CT-Gerätes oder des Labors, sodass keine Diagnostik durchgeführt werden konnte.

Ein ähnliches Konzept wie die MSU-Studie verfolgte die Berliner „Phantom-S–Studie“ (Weber et al. 2013). Ihr Ziel war es ebenfalls die Zeit vom Alarm bis zur Therapie („time-to-needle“) mittels rt-PA zu reduzieren, in dem sie einen mit CT und Minilabor ausgestatteten Rettungswagen einsetzten. In der mit 77 eingeschlossenen Patienten bisher größten Studie konnte die Behandlungsrate mit rt-PA um mehr als die Hälfte von 21 Prozent auf 33 Prozent gesteigert werden und auch die Zeit vom Notruf bis zum Behandlungsbeginn um 25 Minuten auf 52 Minuten reduziert werden. Im Vergleich zu dieser Studie konzentrierte sich das Einsatzgebiet auf die direkte Umgebung der Charité in Berlin Mitte (Maximum 16 Minuten Anfahrtszeit). Darüber hinaus wurde der Krankenwagen von speziell für die Studie geschulten Einsatzkräften gefahren, während diese Studie innerhalb des normalen Routinebetriebes durchführt wurde.

Im Vergleich zu anderen konzentrierte sich diese Studie auf die Erkennung der klinisch am schwersten betroffenen Patienten mit M1/M2-Verschlüsse der ACM, die, bei schneller und zielgerichteter Therapie mit einem deutlich verbesserten Outcome der Patienten einhergehen.

Die intrazerebrale Blutung als wichtigste Differenzialdiagnose zur Vermeidung von Komplikationen bei der Therapie des ischämischen Schlaganfalles gilt oberste Priorität. In unserer Studie waren mit zwei intrazerebralen Blutungen und zwei subduralen Hämatomen im Vergleich zu epidemiologischen Studien nur wenige der neurologischen Symptome hämorrhagischen Ursprunges. Bei einem Patienten mit massiver intrazerebraler Blutung und hohem Glasgow-Coma-Scale (GCS) führte die Verlagerung der ACM durch die Blutung zu einer falsch positiven Diagnose eines ischämischen ACM Verschlusses. Dies hätte aber bei genauer Beachtung des Zanette-Index und des fehlenden hohen Widerstands, welche typisch für einen distalen Verschluss ist, vermieden werden können. Die drei anderen Blutungen zeigten im Ultraschall keinen Verschluss der MCA. Im Allgemeinen ist bei einer typischen hypertensiven Blutung in die Stammganglien eine Verlagerung der ACM ein äußerst unwahrscheinliches Ereignis. Trotzdem sollte in Zukunft versucht werden bereits vor Ort mit Hilfe von Markern wie z.B. dem Gliafserprotein (GFAP)(Foerch et al. 2012) eine Blutung auszuschließen.

Einschränkungen der Studie

Die Einschränkungen unserer Studie sind unter anderem die relativ geringe Zahl der proximalen Gefäßpathologien (ACM und ACI) sowie der Vergleich mit nicht standardisierten Protokollen für die Bildgebung in den zwei aufnehmenden Stroke-Units. Außerdem gab es keine Weiterverfolgung der Patienten, welche wir bereits präklinisch als „nicht Schlaganfall" diagnostiziert hatten und somit konnten die Richtigkeit dieser Diagnosen nicht überprüfen werden. Auch wurde bei der klinischen Untersuchung kein standardisierter Score zur Beurteilung des Schwergrades wie z.B. der NIHSS erfasst. Das Studienkonzept verlangte nicht die Untersuchung des vollständigen Circulus-Willisii bei allen Patienten, wodurch zwei > 80% Stenosen der ACI mit einem möglicherweise hinweisenden „cross-filling-Phänomen" übersehen wurden. Eine weitere Einschränkung ist, dass die Ergebnisse des Ultraschalls mit den CTA oder MRA-Daten verglichen wurden, welche erst zu einem späteren Zeitpunkt erstellt wurden, und somit theoretisch eine zwischenzeitliche spontane Thrombolyse zu einem fehlerhaften Vergleich beider Methoden der Gefäßdarstellung geführt haben könnte.

Ausblick

Ressourcen im Gesundheitswesen sind begrenzt, sodass präklinische Schlaganfallprojekte neben den medizinischen Aspekten auch aus dem sozioökonomischen Standpunkt beurteilt werden (Meyer 2012; Silva et al. 2012). Wenn aktuelle technische Probleme gelöst werden können, bietet die Telemedizin eine schnelle Möglichkeit im Rettungswagen erfasste Daten zur Auswertung und klinischen Beurteilung an einen Schlaganfall-Experten zu übertragen (Liman et al. 2012). Verschiedenste telemedizinische Projekte wie das seit 2003 bestehende TEMPiS-Netzwerk (Telemedizinisches Projekt zur integrierten Schlaganfallbehandlung in Süd-Ost-Bayern) aus Regensburg (Audebert et al. 2006) sind aktuell bereits erfolgreich im Einsatz und unterstützen kleinere nicht- neurologische Kliniken anhand von Videokonferenzen und gemeinsamer Beurteilung der CT-Bilder ob z.B. eine Lysetherapie begonnen werden soll.

In Deutschland wird der transkranielle Ultraschall bereits erfolgreich von medizinisch-technischen Assistenten (MTA) unter Aufsicht eines Neurologen durchgeführt. Um eine telemedizinische Versorgung dauerhaft und flächendeckend anbieten zu können, wird es notwendig sein Rettungsassistenten mit einem speziellen Curriculum auszubilden. Dieses soll die Rettungsassistenten dazu befähigen, bedeutsame neurologische Ausfallserscheinungen des akuten Schlaganfalls zu erkennen sowie auch die Standardschnitte des transkraniellen Ultraschalles sicher zu beherrschen. Mikulik et al. zeigten in einer Pilotstudie, dass ein unerfahrener Rettungsassistent unter der telemedizinischer Anleitung eines erfahrenen Neurologen einen diagnostisch verwertbaren transkraniellen Ultraschall durchführen konnte (Mikulik et al. 2006).

Ziel einer konsequenten Fortführung dieses Projektes wäre, die präklinisch erfassbaren Daten aus neurologischer Untersuchung, Anamnese und Vitalparametern zusammen mit den von einem Rettungsassistenten durchgeführten Ultraschalldaten telemedizinisch an einen spezialisierten Neurologen in einer Stroke-Unit zu übermitteln, um dort die Entscheidung über die gezielte Einlieferung in eine entsprechende Klinik oder ggf. sogar den Beginn einer Therapie treffen zu können.

Eine hoffnungsvolle Therapieoption könnte in Zukunft die Sonothrombolyse darstellen. Die erste große Studie, welche eine erhöhte Rekanalisationsrate von MCA-Stenosen durch den ergänzenden Einsatz von niedrigenergetischem „diagnostischem“ transkraniellen Ultraschall zusammen mit rt-PA darstellen konnte, war die 2004 veröffentlichte CLOTBUST-Studie (Alexandrov et al. 2004). Allerdings wurde der Effekt des niedrigenergetischen Ultraschalles auf die Thrombusauflösung in in-vitro Studien in Frage gestellt (Pfaffenberger et al. 2005). Weitere experimentelle Arbeiten verwendeten deshalb hochenergetischen Ultraschall und konnten damit in vitro eine Auflösung von Fibrinthromben erreichen (Siddiqi et al. 1998). Ein Versuch einer multizentrischen randomisierten klinischen Studie mit einem „Sonothrombolyse-Schallkopf“ mit höheren Energien und niedrigeren Frequenzen für die verbesserte Durchdringung des Schädelknochens, musste wegen einer erhöhten Hirnblutungsrate abgebrochen werden

(TRUMBI) (Daffertshofer et al. 2005). Dieser Effekt konnte in der Folgezeit in Metaanalysen ähnlicher Studien zur Sonothrombolyse unter Verwendung anderer Energien glücklicherweise nicht verallgemeinert werden. (Tsivgoulis et al. 2010)

Ein weiterer erfolgreicher Ansatz im Tierexperiment ist die Verwendung von Ultraschallkontrasmittel um den Thrombus ohne den zusätzlichen Einsatz von rt-PA auflösen zu können. Hierdurch könnten die Probleme wie Kontraindikationen, Zeitfenster und Verfügbarkeit von rt-PA umgangen werden.

Pathophysiologischer Hintergrund ist, dass die i.v applizierten Mikrosphären durch den Ultraschall zum Schwingen oder Platzen gebracht werden und somit die Energie des Schalls verstärken und der Thrombus dadurch aufgelöst wird (Culp et al. 2011; Hölscher et al. 2011; Hölscher et al. 2013).

Diese Studie zeigt die hohe diagnostische Genauigkeit des transkraniellen Ultraschalles auch unter erschwerten prähospitalen Bedingung. Momentan ist die Wertigkeit der Diagnostik noch angewiesen auf das Know-how von auf Schlaganfall spezialisierten Neurologen, einschließlich ihrer Fähigkeit, transkraniellen Ultraschall in einer Vielzahl von unterschiedlichen Positionen durchführen zu können und auch die Ergebnisse der neurologischen Untersuchung vor Ort mit den Ultraschallergebnissen korrelieren zu können. Mit dem zukünftigen Einsatz von telemedizinischer Datenübertragung, dem konsequenten Einsatz von Kontrastmitteln, der speziellen Ausbildung für Rettungsdienstpersonal sowie erfolgreichen Phase-III-Studien zur Sonothrombolyse könnte in der Zukunft eine sehr frühe therapeutische Option für die Behandlung von schweren Schlaganfällen für die breite Bevölkerung zu Verfügung stehen.

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Eidesstattliche Erklärung

Hiermit erkläre ich, dass ich die vorliegende Arbeit ohne unzulässige Hilfe Dritter und ohne Benutzung anderer als der angegebenen Hilfsmittel angefertigt habe. Die aus anderen Quellen direkt oder indirekt übernommenen Daten und Konzepte sind unter Angabe der Quelle gekennzeichnet. Insbesondere habe ich nicht die entgeltliche Hilfe von Vermittlungs- bzw. Beratungsdiensten (Promotionsberater oder andere Personen) in Anspruch genommen. Niemand hat von mir unmittelbar oder mittelbar geldwerte Leistungen für Arbeit erhalten, die im Zusammenhang mit dem Inhalt der vorgelegten Dissertation stehen. Die Arbeit wurde bisher weder im In- noch im Ausland in gleicher oder ähnlicher Form einer anderen Prüfungsbehörde vorgelegt.

Augsburg, 14.11.2014

Moriz Herzberg

Anhang

- Critical Ultrasound Journal: „Prehospital stroke diagnostics based on neurological examination and transcranial ultrasound“

- Cerebrovascular Diseases: „Transcranial ultrasound from diagnosis to early stroke treatment – Part 2: Prehospital neurosonography in patients with acute stroke – The Regensburg Stroke Mobile Project“

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Prehospital stroke diagnostics based on neurological examination and transcranial ultrasound

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Abstract

Background: Transcranial color-coded sonography (TCCS) has proved to be a fast and reliable tool for the detection of middle cerebral artery (MCA) occlusions in a hospital setting. In this feasibility study on prehospital sonography, our aim was to investigate the accuracy of TCCS for neurovascular emergency diagnostics when performed in a prehospital setting using mobile ultrasound equipment as part of a neurological examination.

Methods: Following a '911 stroke code' call, stroke neurologists experienced in TCCS rendezvoused with the paramedic team. In patients with suspected stroke, TCCS examination including ultrasound contrast agents was performed. Results were compared with neurovascular imaging (CTA, MRA) and the final discharge diagnosis from standard patient-centered stroke care.

Results: We enrolled '232 stroke code' patients with follow-up data available in 102 patients with complete TCCS examination. A diagnosis of ischemic stroke was made in 73 cases; 29 patients were identified as 'stroke mimics'. MCA occlusion was diagnosed in ten patients, while internal carotid artery (ICA) occlusion/high-grade stenosis leading to reversal of anterior cerebral artery flow was diagnosed in four patients. The initial working diagnosis 'any stroke' showed a sensitivity of 94% and a specificity of 48%. 'Major MCA or ICA stroke' diagnosed by mobile ultrasound showed an overall sensitivity of 78% and specificity of 98%.

Conclusions: The study demonstrates the feasibility and high diagnostic accuracy of emergency transcranial ultrasound assessment combined with neurological examinations for major ischemic stroke. Future combination with telemedical support, point-of-care analysis of blood serum markers, and probability algorithms of prehospital stroke diagnosis including ultrasound may help to speed up stroke treatment.

Keywords: Acute stroke; Emergency medicine; Prehospital diagnostics; Transcranial neurosonography; Mobile health unit

Background

Ischemic stroke is a time-critical vascular disease that affects neural function and is the leading cause of permanent disability in people in industrialized nations [1,2]. Although the ECASS 3 trial widened the time window for intravenous (IV) thrombolysis to 4.5 h [3] and this window may be extended in selected patients undergoing interventional thrombectomy [4], the majority of patients do not benefit since fewer than 25% of patients arrive within 2 h of symptom onset [5] and only 36% arrive within 3 h (Bavarian Society for Quality control 2012 report) [6]. Significant prehospital delays are the main reason why patients do not receive effective treatment [2,7,8]. Recent analyses from previous studies demonstrate a total median prehospital delay varying between 35 and 71 min [9,10]. Ideally, this time period may be devoted for diagnostics, early allocation to an appropriate hospital, and initiation of stroke-specific therapies [11-13].

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Transcranial color-coded sonography (TCCS) is a feasible, fast, and non-invasive bedside method for the evaluation of cerebral arteries in acute stroke, and it is a routine tool in most stroke units. Particularly when contrast agents are applied, TCCS is valid compared with computed tomography (CT) angiography [14] and magnetic resonance angiography (MRA) [15] for the diagnosis of arterial occlusions in patients with acute ischemic stroke, especially in middle cerebral artery (MCA) obstructions [16]. According to the 'Neurosonology in Acute Ischemic Stroke study', TCCS is an independent predictor for stroke patient's outcome [17]. Assessment of vascular pathology and hemodynamics in patients with acute stroke is thought to enable early judgment of functional outcome and thrombolytic efficacy and could identify patients who might benefit from interventional treatment [18-20]. In our study, we focused TCCS examination on the detection of middle cerebral artery occlusion in its proximal segment (M1-MCA occlusions) - the most common site for cerebral artery occlusions - since we hope to shorten time from symptom onset to beginning of therapy with a very early diagnostic approach.

Goal of this investigation

In this 'Regensburg stroke mobile project', we hypothesized that a neurologist equipped with a portable ultrasound device is able to achieve a similar diagnostic accuracy 'in the field' as compared with in-hospital advanced neuroimaging (CTA, MRA).

Methods

Study design

We describe a single-site prospective study in which we compare the results of preclinical neurological examinations supported by TCCS in the field with the results of standard stroke imaging studies (CTA, MRA) and with final discharge diagnoses from the treating stroke unit. In the hospital, standard stroke care was applied without a dedicated imaging or treatment algorithm. In this regard, prehospital TCCS was performed to confirm or deny the presence of major intracranial artery occlusions and not to detect intracranial hemorrhage. Despite the non-invasive nature of the study, we obtained written informed consent from the patient or the next available relative. The study was approved by the local ethics committee (Ethic committee Nr. 09/135) and was performed in accordance with guidelines set out in the Declaration of Helsinki.

Setting

The diagnostic portion of the study was performed between May 2010 and January 2011 in the city and rural district of Regensburg. This region supports a population of approximately 150,000 people in east Bavaria, Germany; the operational area that we covered extended up to 35 km in radius (Figure 1).

Selection of participants

Patient enrollment took place during regular work hours (8 a.m. to 4:30 p.m.), Monday through Friday. Patients were enrolled consecutively and unselected by the dispatch center. The dispatch center did not follow dedicated inclusion criteria but decided following its internal routine algorithms. After the dispatch center received a '112' stroke call (the German equivalent for a '911' stroke call in the USA), the ambulance team (emergency physician and paramedic) and the stroke team (a stroke- and TCCS-experienced neurologist and a paramedic driver in a BMW series 1, dedicated 'stroke mobile') were both alerted and sent to the site of the incident. After first aid had been provided to the patient and vital parameters had been stabilized, a brief neurological examination was performed. No TCCS was performed if no neurological symptoms suggestive for acute stroke or transient ischemic attack (TIA) were present. In such cases or if the patient did not show any neurological symptoms, patients either stayed at home or were transferred to the nearest emergency medical department. These cases were not included in the study follow-up. All patients who presented symptoms indicating probable or definite acute stroke were included in this analysis.

Interventions

In all patients with symptoms of an acute stroke, neurological examination was immediately followed by a TCCS assessment. Neurological examination was based on a simplified and structured assessment including paresis in face, arm, and leg; speech disorders; consciousness; and gaze palsy. Symptoms indicating probable or definite acute stroke were defined as one positive symptom with acute onset. Additionally acute stroke was proposed if the neurologist had the suspicion of stroke due to symptoms like dizziness, hemianopia, and related symptoms.

The highest priority in all cases was to avoid any delay before hospital admittance. Ultrasound examination took place either at the site of the initial treatment (for example, at the patient's couch, on the floor, or at bedside) or during ambulance transport. All neurological patients were transferred to a specialized stroke unit. All patients underwent emergency diagnostic examinations consisting of non-contrast brain CT and, if necessary, CTA and MRA. The primary vascular diagnostic method was chosen based on the patient's level of consciousness, comorbidities (for example, a cardiac pacemaker was a contraindication for magnetic resonance imaging (MRI)), and severity of symptoms. The final diagnosis was made by the responsible stroke team neurologist based on all available clinical information and the contents of the

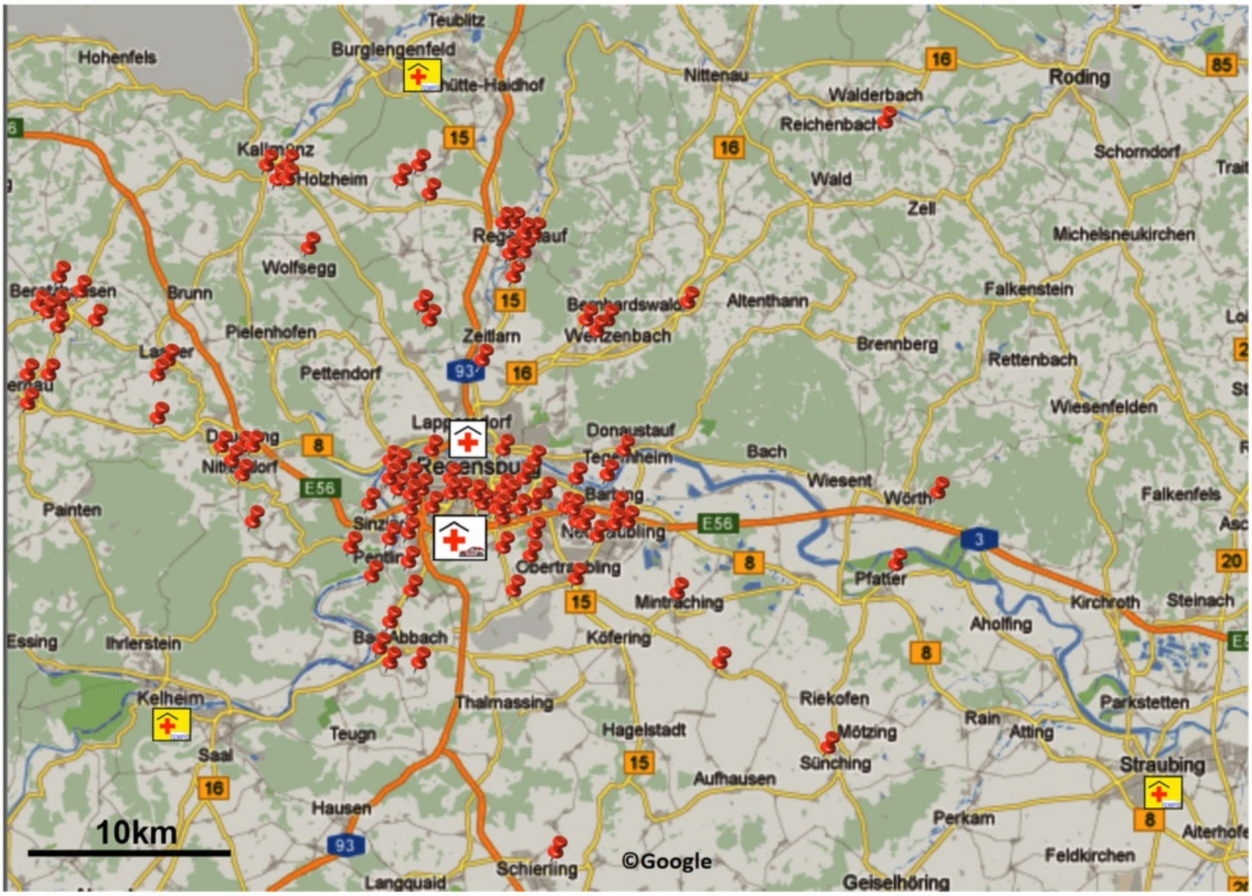

Figure 1 Map showing Regensburg and the surrounding area. Pins indicate sites of emergency calls. The Regensburg stroke mobile was housed at the stroke unit of the Department of Neurology, Bezirksklinikum Regensburg. The second stroke unit in Regensburg is located at the Department of Neurology, Krankenhaus Barmherzige Brüder Regensburg. Three telemedical stroke units within the TEMPiS network are located near Regensburg. Bar indicates 10 km (Google©).

patient's medical record. Patients in whom imaging studies provided evidence of cerebral infarction were given a final diagnosis of ischemic stroke, even if their neurological deficits were transient. A diagnosis of TIA was given to patients in whom deficits lasted less than 24 h, and there was no imaging evidence of infarction. To allow a comparison between standard imaging methods and TCCS, patients who received IV thrombolysis were only included if they had undergone at least one vascular imaging study before IV thrombolysis.

Ultrasound equipment and data acquisition

We used two portable color duplex ultrasound machines equipped with a phased array transducer capable of transcranial imaging: SonoSite Micromaxx® with a P17 transducer (SonoSite Inc., Bothell, WA, USA) and Philips CX50® with a P2-5 transducer (Philips Ultrasound, Bothell, WA, USA). The standard setting with a transmission frequency of 2.0 MHz for brightness, color, and Doppler mode was used on both machines. Images were stored as bitmap (Micromaxx®) and DICOM (CX50®) files on the hard drive and converted later to jpg files for data transfer and off-line analysis.

An ultrasound contrast agent (UCA; SonoVue®, Bracco Imaging SpA, Milan, Italy) was administered intravenously via a peripheral vein primarily in cases in which the quality of the transcranial bone window was deemed inferior and an urgent diagnosis needed. Intravenous injections of 0.5 to 2 ml UCA were administered, depending on the quality of the temporal bone window, as previously described [21]. After identification of the best temporal bone window, the protocol required color-mode visualization and confirmatory flow measurements in the proximal M-1 segment of both MCAs using spectral Doppler ultrasonography. Angle correction was not performed. The examiner could decide whether to extend the protocol to measurements in the anterior and posterior cerebral arteries (ACAs and PCAs, respectively). Proximal MCA occlusions were diagnosed when the ipsilateral ACA and/ or the contralateral ACA and MCA could be visualized and imaging confirmed the existence of a sufficient temporal bone window with or without UCA. Distal MCA or MCA branch occlusions were defined according to criteria published by Zanette and coauthors [22]. The TCCS examination time was defined as the time between the first and last image, as documented in the imaging files. Pathological disorders of the internal carotid artery (ICA) were suspected in either the absence of ipsilateral ACA and MCA flow or a reversal of flow in the ACA that was suggestive of >80% stenosis or total occlusion of the ICA [23]. All TCCS examinations were reviewed by an experienced sonographer who is certified by the German Society of Ultrasound in Medicine (FS, DEGUM Stage III).

Outcome - primary end point

Primary end point of this study is accuracy of TCCS compared to the 'gold standard' neurovascular imaging (CTA/MRA).

Outcome - secondary end point

Secondary end points include accuracy of initial working diagnosis compared to discharge diagnosis. Safety aspects are side effects of contrast agent.

Primary data analysis

A simplified data collection sheet was used, which notes the timing of emergency call, arrival at the patient's side, and patient handover to hospital staff; timing of ultrasound examination and whether visualization of both MCAs had been achieved; final diagnosis after the patient was discharged from the hospital; and documentation of stroke treatment used. Data derived from neurovascular imaging studies, such as CTA, MRA, or in-house neurosonography, were collected and correlated to the results of the prehospital TCCS study. The distance from base hospital to the patient was calculated by the navigational system, and values are given as median values with standard deviations.

Sensitivity analyses

Based on the clinical and TCCS data leading to a prehospital diagnosis and the final discharge diagnosis, we calculated the sensitivity, specificity, and positive and negative predictive values as well as the respective 95% confidence intervals (CIs) of the procedure in determining stroke vs. mimic. Based on the TCCS data, we calculated the same statistics for determining occlusion of the MCA. All data were entered into an Excel worksheet and calculated using MedCalc (version 11.6.1; http://www.medcalc.org).

Results and discussion

Results

Characteristics of study subjects

Table 1 lists baseline demographic characteristics. We received 232 emergency calls and rendezvoused with the first aid team at the patient's site. We excluded 119 patients because their initial clinical examinations did not show stroke or neurological symptoms but instead suggested other disorders. These patients were not examined using TCCS. Another 11 patients were excluded after the emergency doctor and stroke neurologist excluded acute stroke plus TCCS indicated normal intracranial arterial flow. These patients were transferred to general emergency departments, and some were in hospitals without a stroke unit or even stayed at home. There was no follow-up on these patients. The time used to perform the ultrasound examination was 5 min and 36 s. (mean, SD ± 2 min and 12 s).

Stroke diagnosis - overall sensitivity and specificity

Of the 102 patients included in the study, 73 (72%) received a confirmed diagnosis of stroke by their treating hospital neurologists and 29 (28%) were correctly

Table 1 Baseline characteristic of the study sample and examiner, location, and time to ultrasound

Characteristic	Value
All patients, *n*	232
Patients included, *n*	102
Sex (female/male)	54/48
Mean age (SD)	76.8 (13.41)
Ultrasound examination time (mean, SD)	5 min, 36 s (2 min,12 s)
Alarm-to-handover duration (mean, SD)	65 min (25 min)
Contrast enhanced TCCS, *n*	41
Distance to hospital, km	10 (2–41)
Clinic admission, *n* = 102	
Stroke unit	98
Internal Medicine	3
Telemedicine Stroke unit	1
Examining physician	
Investigator 1	57
Investigator 2	42
Investigator 3	3
Site of ultrasound investigation	
Patient's home	51 (50%)
During transport in ambulance car	43 (42%)
Private office practice	4 (4%)
Public space	2 (2%)
Senior citizen home	2 (2%)

TCCS, transcranial color-coded sonography; SD, standard deviation.

classified as stroke mimics. In the field, 4 patients were given the misdiagnosis of a non-stroke event (4%), whereas 15 patients (15%) received the misdiagnosis of stroke when their symptoms merely mimicked those of a stroke. In summary, the initial working diagnosis prior to patient admission to the hospital showed a sensitivity of 95% (95% CI 86 to 98) and a specificity of 48% (29 to 67) in the hospital workup (Tables 2, 3, and 4). Two examples of stroke mimics with interesting neurosonographic findings (normal flow but indications for subdural hematoma or midline shift) were found in a patient with a subdural hematoma (Figure 2) and a brain tumor (Figure 3). In 68% of the patients, stroke-like symptoms were caused by ischemic stroke/TIA with suspected etiology of large artery atherosclerosis in 50% followed by cardioembolism and small vessel disease (Table 5). Only 5% of symptoms were caused by any intracranial hemorrhage. During the study period, 9 of 50 patients (18%) received IV thrombolysis and 1 patient underwent mechanical thrombectomy.

Transcranial color-coded duplex sonography in the field

Ultrasound contrast agents were administered in 41 patients (40%), and no adverse event was noted. Despite the use of UCA, inferior temporal bone windows were found in 11 of the 102 patients (11%) (in 5 patients bilaterally, in 6 patients unilaterally), and these were excluded from further analysis testing sensitivity and specificity of prehospital TCCS. An additional patient was excluded who presented with MCA occlusion with related hemiparesis and spontaneous thrombolysis during transport. One patient with a non-stroke diagnosis (temporal arteritis) and three patients with unremarkable neuroimaging findings yet stroke diagnosis at discharge were also excluded.

Table 2 Initial working diagnostic

Stroke ($n = 102$)	Stroke mimics
Proved right ($n = 69$)	$n = 3$ exsiccosis
	$n = 2$ hypoglycemia
	$n = 2$ syncope
	$n = 1$ pneumonia
	$n = 1$ migraine
	$n = 1$ slipping
	$n = 1$ persisting atrial fibrillation
	$n = 1$ functional brachiofacial hemiparesis
	$n = 1$ hypertensive rise
	$n = 1$ epileptic seizure
Proved wrong ($n = 4$)	$n = 5$ epileptic seizure
	$n = 4$ tumor
	$n = 2$ subdural hematoma
	$n = 1$ exsiccosis
	$n = 1$ MI + brain concussion
	$n = 1$ metabolic encephalopathy
	$n = 1$ peripheral nerve compression (C7)

Table 3 Preclinical working and discharge diagnostics

		Discharge diagnostic		
		Stroke	Stroke mimic	Total
Preclinical working diagnostic	Stroke	69	15	84
	Stroke mimic	4	14	18
Total		73	29	102

The flow diagram (Figure 4) shows the diagnostic pathway and the neurovascular imaging reference methods obtained as ‘gold standard in hospital’. In 4% of patients, diagnosis of stroke was first detected by non-contrast CT (cerebral computed tomography (CCT)). In 7% of patients, CTA imaging first led to the final diagnosis.

Preclinical TCCS demonstrated 12 occlusions or high-grade stenoses of major brain-supplying arteries (MCA and ICA) including 10 M1-MCA occlusions. Internal carotid artery (ICA) occlusions were diagnosed when reversed flow (‘cross-filling’) occurred in the ipsilateral ACA; this finding is indicative of >80% stenosis or total occlusion of the ICA according to the ECST criteria [24]. Standard imaging studies (CTA, MRA, and CCT) showed 14 major cerebral artery occlusions: 10 involving the MCA and 4 involving the ICA (Table 6). In the early days of the study, a PCA was mistaken to be a patent MCA in one patient when the UCA was incorrectly injected through a filter system, resulting in the destruction of microbubbles and inferior image quality. Also, TCCS resulted in the misdiagnosis of distal MCA occlusion in one patient, according to the Zanette index [22]. In this patient, an atypical parieto-occipital intracerebral hemorrhage (ICH) caused dislocation of the MCA, which led to a near-perpendicular angle of insonation. In retrospect, considering the lack of resistance in the low-flow profile and use of the UCA may have helped avoid the misdiagnosis (an example of a correct diagnosis of distal MCA occlusion is shown in Figure 5). Two >80% stenoses or total occlusions of the ICA were not detected; in those cases, the examiner investigated both MCA arteries according to the study protocol but did not examine the ACA and, therefore, missed a cross-filling phenomenon (Figure 6). In summary, we found a sensitivity of 90% and specificity of 98% (positive predictive value 90%, negative predictive value 98%) in achieving a correct diagnosis of MCA occlusion.

Table 4 Sensitivity, specificity, positive predictive value, and negative predictive value

	SE (95% CI)	Sp (95% CI)	PPW (95% CI)	NPW (95% CI)
Stroke vs. mimic	94% (86 to 98)	48% (29 to 67)	82% (72 to 89)	77% (52 to 93)

SE, sensitivity; Sp, specificity; PPW, positive predictive value; NPW, negative predictive value.

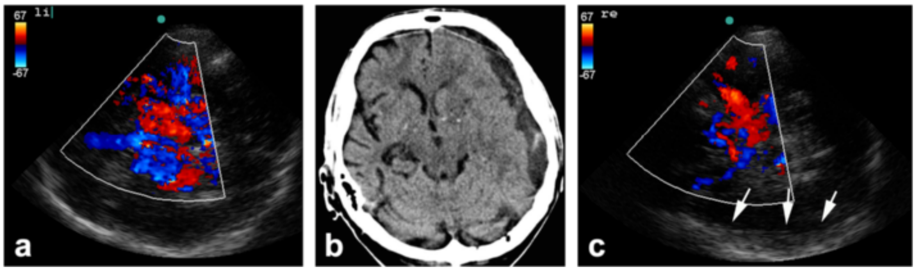

Figure 2 Left-sided subdural hematoma in an 80-year-old patient. (a) TCCS performed 30 min after onset of sensory aphasia shows a patent left MCA and the complete circle of Willis. **(b)** Cranial CT scan demonstrates a subdural hematoma (SDH), and **(c)** when viewed in retrospect, TCCS from the right side reveals the SDH in the contralateral hemisphere in B-mode (arrow). The patient's medical history included hypertension, diabetes, and a fall 2 days earlier.

Patent MCAs, as demonstrated on standard neurovascular imaging studies (CTA, MRA) in the hospital, were diagnosed correctly in 75 of 76 cases in which an ischemia in any of the MCA territories was suspected and in 71 of 72 cases in which an ischemic stroke of the MCA-M_1 and ICA was suspected (Table 6). One false-negative ICA stenosis could be identified on CTA scans. Two large hypodense areas indicated another false-negative ICA and an MCA mainstem occlusion. In one patient, in whom an atypical frontal ICH caused severe left-sided hemiparesis, a clinical syndrome potentially attributed to MCA occlusion, normal flow in the MCA was observed and confirmed by CTA. However, in addition to a diagnosis of major vessel occlusion, TCCS supported the likelihood of cerebral ischemia, as demonstrated in a patient in whom the first diagnosis was tachycardiac atrial fibrillation resulting in a changing peak systolic flow pattern (Figure 7).

Discussion

In this study, we evaluated the potential of prehospital stroke assessment when an emergency doctor is joined at the scene of the event by a stroke neurologist equipped with a mobile ultrasound system for transcranial vascular diagnostics. More than half of the patients seen after a stroke emergency call were identified as not suffering a stroke by virtue of 'neurological eyeballing'. The remaining patients who underwent combined neurological and neurosonological examinations were identified as having a stroke with a sensitivity of 94% and a specificity of 48%. This seemingly disappointing result is counterbalanced by high diagnostic sensitivity and specificity in patients with MCA occlusions (90% sensitivity and 98% specificity) or combined pathology in the anterior circulation for which the study was not designed (78% sensitivity and 98% specificity).

Prehospital stroke diagnosis

The high percentage of patients (56%, 130 of 232 patients) who were excluded from the study because they had no neurological symptoms shows the difficulty faced by dispatch center staff in distinguishing between stroke and non-stroke symptoms based on a telephone call. In the current setting, an experienced neurologist performed an individual and focused neurological examination in addition to a neurovascular diagnosis in the emergency setting using TCCS. Further improvement may be added by systematically adding data of other findings (atrial

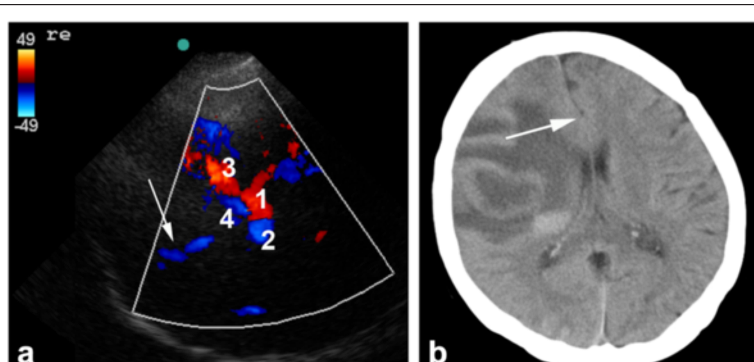

Figure 3 Images obtained in a 54-year-old patient with progressive left-sided paralysis due to a brain tumor. (a) TCCS revealed patent arteries, but the midline has shifted as seen in a non-optimal temporal bone window during CT. (1) ipsilateral and (2) contralateral posterior cerebral artery, (3) ipsilateral middle cerebral artery, and (4) ipsi- and contralateral anterior cerebral arteries **(b)** with shift to the contralateral side (arrow).

Table 5 Final diagnosis and etiology at discharge

Final diagnosis (n = 102)		Territory		Etiology (TOAST)	Percentage
TIA	n = 20	Anterior circulation	n = 58	Large artery atherosclerosis	50
Ischemic stroke	n = 50	Posterior circulation	n = 12	Cardioembolism	24
Hemorrhagic stroke	n = 3			Small vessel occlusion	13
Subdural hematoma	n = 2			Stroke of other etiology	4
No stroke	n = 27			Stroke of undetermined etiology	9

fibrillation, list of medications, medical history) to combine to a probability model for stroke occurrence.

A delay of prehospital time is counterproductive in efficient stroke treatment. Therefore, the emergency teams were advised not to wait for the stroke mobile. Furthermore, examination and all associated acts were done during transport and at the site of initial treatment only if primary care was ongoing and not disturbed by neurological or ultrasound examination.

Diagnostic accuracy of neurovascular imaging

Initiation of stroke-specific therapies first requires a battery of diagnostic tests with the major focus on excluding the presence of ICH. Here, sensitivity of CCT is beyond

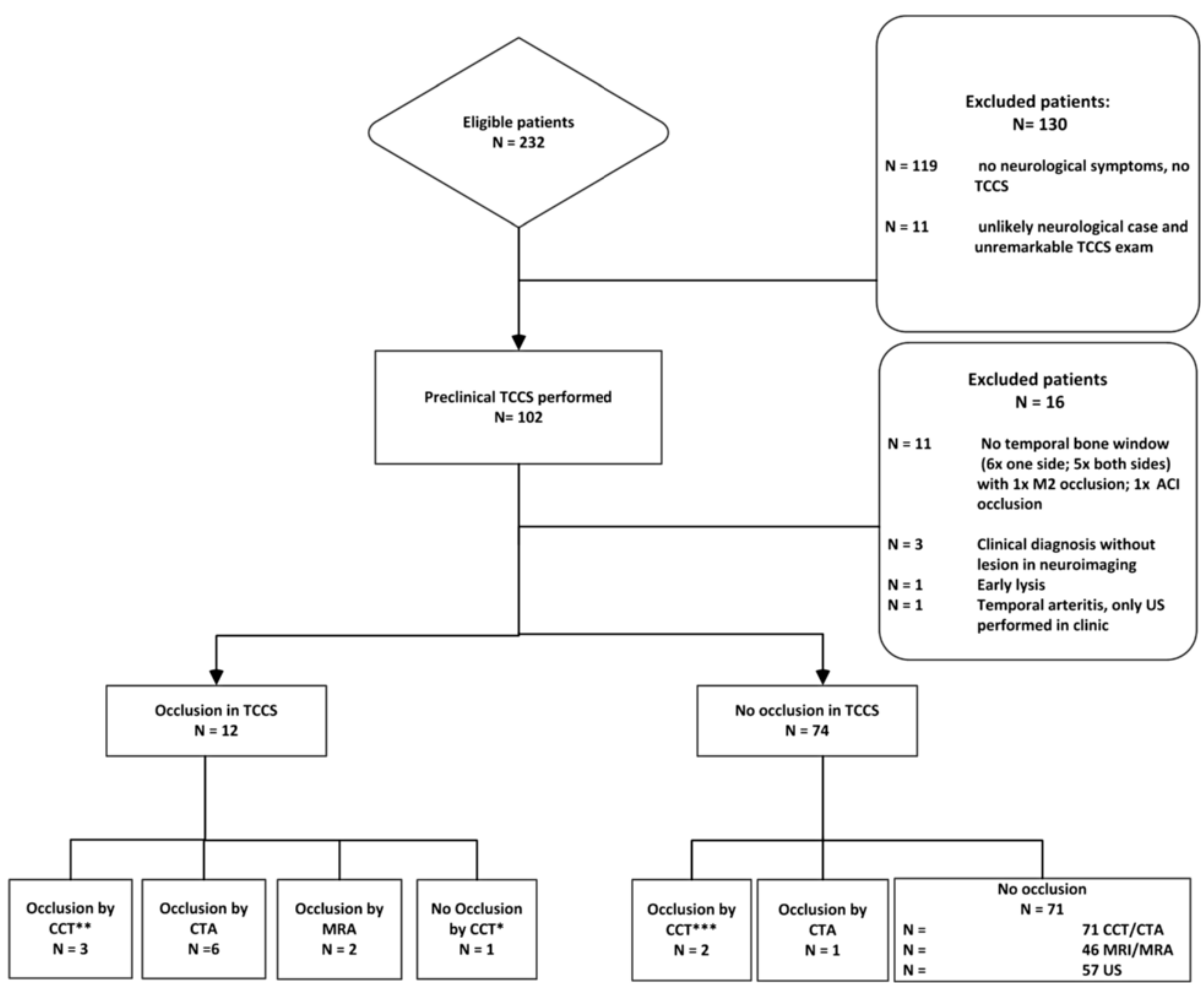

Figure 4 Flow diagram showing the diagnostic imaging pathway used to diagnose ischemic stroke. It includes the diagnostic accuracy for M1 and ICA pathology. US, ultrasound of intra- and extracranial arteries; TCCS, transcranial color-coded sonography; M1, middle cerebral artery mainstem; ICA, internal carotid artery.

Table 6 Diagnostic accuracy TCCS

		Standard stroke imaging[a]		Total
		Occlusion	No occlusion	
MCA mainstem and ICA				
Preclinical TCCS	Occlusion	11	1[b]	12
	No occlusion	3[c]	71	74
Total		14	72	86
MCA occlusion				
Preclinical TCCS	Occlusion	9	1[b]	10
	No occlusion	1[d]	75	76
Total		10	76	86

[a]CTA, MRA, and CCT according to diagnostic pathway in stroke unite; [b]massive intracerebral hemorrhage (ICH) described as distal MCA occlusion; [c]no ACA imaged and therefore 2 ICA occlusions or >80% stenosis with cross-filling missed; [d]contrast through filter, and PCA described instead of MCA occlusion. CTA, computed tomography angiography; MRA, magnetic resonance angiography; CCT, cerebral computed tomography; ACA, anterior cerebral artery; ICA, internal carotid artery; MCA, middle cerebral artery; PCA, posterior cerebral artery.

controversy [25]. Comparing the state-of-the-art stroke imaging modalities, MRI and diffusion weighted imaging (DWI) show the best sensitivity and specificity and DWI additionally has a very good predictive value for the 'penumbra' [26,27]. Unfortunately, in the real world, only 14% receive an MRI in the emergency department (ED) and only 29% within the first 12 h [28]. As CTA is not being obtained routinely, many physicians in EDs rely on CCT only. However, CCT alone shows a low sensitivity for ischemic stroke detection (sensitivity 27% to 64%) [29-32] and has a mean sensitivity for early infarction sign detection of 66% (20% to 87%) with a specificity of 87% (56% to 100%). One can argue however that ischemic stroke can be treated within the first 4.5 h of stroke onset using recombinant tissue plasminogen activator (rtPA on the basis of minimal imaging information (i.e., the exclusion of brain hemorrhage with CT), and therefore, the high sensitivity of CT for hemorrhage makes standard CT an important technique for the assessment of patients with acute stroke.

On the other hand, rtPA alone shows a low rate of acute recanalization particularly in proximal vessel occlusion (distal ICA 4.4%; M1-MCA (32.3%); M2-MCA (30.8%)) which is significantly improved only with an endovascular

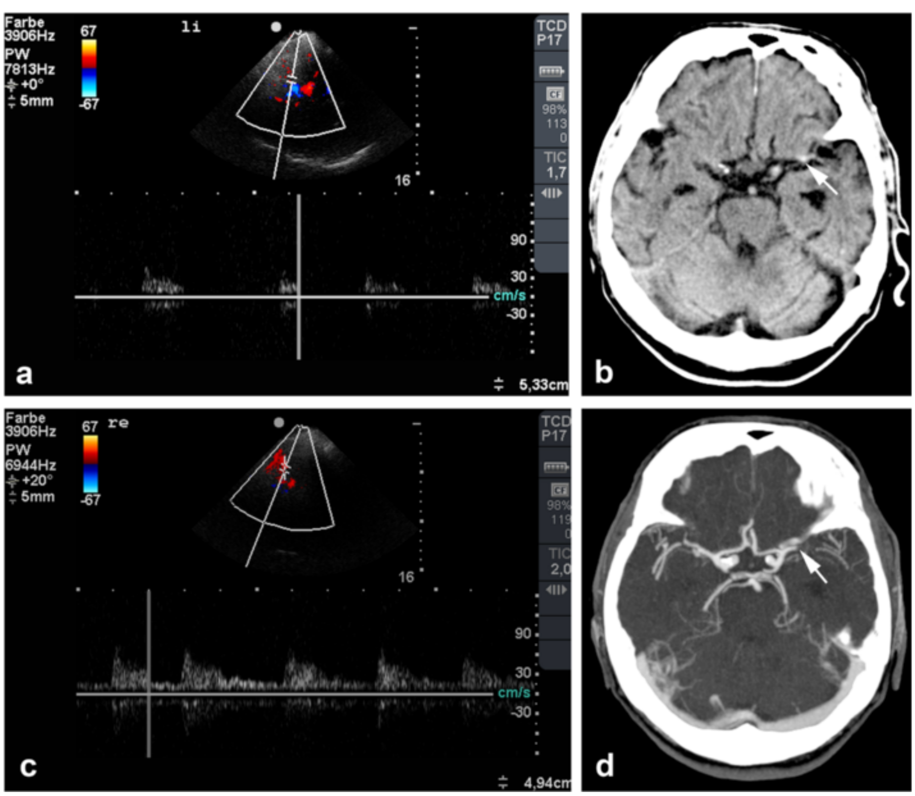

Figure 5 Distal MCA mainstem occlusion in a patient with global aphasia and right-sided hemiparesis. (a) Prehospital TCCS showed a resistance profile only at the origin of the left MCA, **(b)** whereas flow in the contralateral MCA was unremarkable. At the hospital, **(c)** a CT scan displayed a dense artery sign (arrow), and **(d)** a CTA showed occlusion of the MCA (arrow).

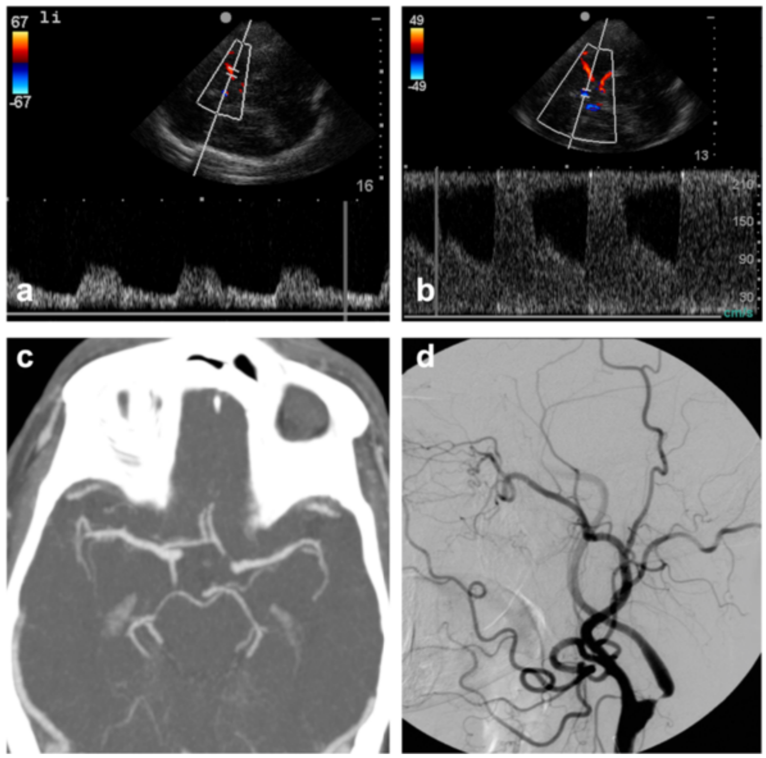

Figure 6 Cross-filling suggestive of high-grade stenosis or occlusion of the ICA. Images obtained in a 73-year-old patient suffering from a TIA with a 5-min-long paresis of the right leg. During transport, the patient's high blood pressure and angina pectoris prompted a decision to admit him to the Department of Cardiology. The results of the TCCS changed that decision, however, and the patient was admitted to the Stroke Unit. Surgery was performed the following day. **(a)** TCCS reveals normal flow in the left MCA. **(b)** Flow in the left ACA was increased and retrograde, suggesting collateral filling through the anterior communicating artery. **(c)** CT-angiography shows patency of all intracranial arteries but lacks flow information. **(d)** DSA on the same day confirms a tight, high-grade stenosis at the origin of the left ICA.

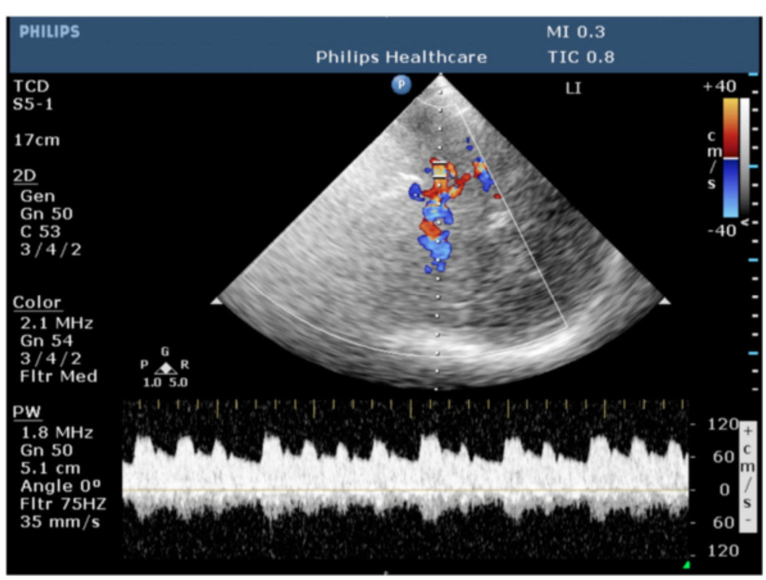

Figure 7 TCCS with Doppler spectrum revealing tachyarrhythmia with changing cardiac output volumes in a 50-year-old patient. The patient experienced 5 h of mild facial paralysis and weakness of the left arm. MRI confirmed a small cardioembolic right MCA infarction (not shown).

or combined ('bridging') approach [33-35]. Even though recent trials question the long-term benefit of an interventional approach in general, they on the one hand do show benefit for the subgroups we focused on (M1, carotid T) [36]. On the other hand, they stress the need for very early diagnosis, since even a 1-h delay in the time to treatment negates the benefit of a higher recanalization rate with endovascular treatment [37].

Bedside transcranial ultrasound has proved its high agreement with CTA studies, good identification of vessel occlusions amenable for interventional treatment, and good predictive values for the outcome of the patient in several studies [16,17,38].

In our study, TCCS in the field and with portable small ultrasound machines was performed with high accuracy by experienced investigators and showed an almost similar diagnostic accuracy compared with those of previously published studies performed in a hospital setting, in which blinded TCCS was compared to the reference method [14]. Yet, the variety of positions in which the patient had to be examined in different settings required substantial experience and dexterity on the part of the investigator, so in the future, some certification may be advised for this specific application.

Prehospital stroke projects

A variety of prehospital stroke projects are currently underway. Examples include the Stroke Angel project [39], STEMO [40], Mobile Stroke Unit (MSU) [41], Aster (www.aster-magdeburg.de), and Med-on-@ix [42] projects. All these projects differ in concept, personnel required, timelines, and costs.

The current MSU concept aims to bring guideline-adherent stroke treatment directly to the emergency site using a specialized ambulance equipped with a CT scanner, point-of-care laboratory and a telemedicine connection to the hospital (ClinicalTrials.gov identifier: NCT00792220). They could significantly reduce the time from alarm to therapy decision from 76 to 35 min in the MSU group. However, distances to hospital differ (6 km (4 to 10) vs. 8 km (6 to 15) in control group) and are much shorter than in our study (10 km (2 to 41). Unavailable diagnostic equipment in 18% (22 of 122) due to technical problems with the CT scanner or the laboratory was comparable to 10% exclusions due to insufficient temporal bone window. Bringing CT diagnostic to the patient is, from our point of view, not applicable in rural areas due to long distances and extensive costs.

A study related to MSU represents the Phantom-S Study [43]. Their aim is to reduce alarm-to-needle time by the implementation of a CT scanner, teleradiological support, and point-of-care-laboratory-equipped ambulance. In comparison to our study, the covered region is limited to a maximum of 16 min from dispatch to arrival at the patient within central Berlin. Furthermore, the ambulance staff was specially trained for the study, whereas we implemented our study within normal routine emergency medical services (EMS). This approach will be most effective within urban centers.

Compared to others, we focused on ischemic stroke of proximal M1/M2 occlusions leading to the clinically worst outcome but with relatively good prognosis if treated by experts timely and therefore crucial to be detected and streamlined to a specialized stroke unit early [33]. In comparison to other projects, our focus was not only on metropolitan areas but also on rural areas with long distances to the next stroke unit (Figure 1). We found that in-field use of mobile ultrasound systems does not result in prolonged prehospital delays and is particularly suited in patients with large arterial occlusions. Mobile ultrasound showed an overall sensitivity of 78% and specificity 98% for 'major MCA or ICA' occlusions. Our primary aim in this study was to detect vessel occlusions and not to exclude brain hemorrhage with the use of ultrasound. In order to initiate, i.e., thrombolysis cases of hemorrhagic stroke and stroke mimics (Tables 2, 3, and 4) must be excluded and must still require profound diagnostics at specialized stroke units. Despite a high likelihood of ischemic stroke in cases of MCA occlusion detected by prehospital TCCS, additional tools such as point-of-care serum stroke diagnostics are needed in the future before prehospital thrombolysis.

Another aspect of prehospital cerebrovascular diagnostics is the lack of comparative prehospital data. Neither data on diagnostic accuracy nor the percentage of CTAs performed in the publications of other mobile stroke units using a CT scanner is available; thus, comparison of diagnostic accuracy of prehospital TCCS is limited.

The combination of the different experiences gained by the various preclinical stroke treatment studies could be used to implement a reliable telemedical tool to detect and treat stroke patients in a countrywide manner.

Limitations of the study

The limitations of our study are the relatively low number of proximal large vessel pathology (MCA and ICA) and no standardized stroke neurovascular diagnostic algorithm in the two receiving stroke units. The latter is due to the fact that stroke treatment has different diagnostic algorithms depending on a variety of factors such as time window, age, and availability of stroke MRI, among others - a drawback common in health-care research. Furthermore, we did not pursue contact with the patients we 'eyeballed' as suffering from something other than stroke and thus did not compare our initial prehospital diagnosis with the final diagnosis in these patients. We examined fewer than half of our patients using the contrast agent thus explaining the high number of patients with insufficient temporal bone windows (11%). The study concept did not require to always examine the complete circle of Willis in all patients, leading to two missed >80% ICA stenosis with cross-filling phenomena documented in stroke unit TCCS. A further limitation is that findings from ultrasound were compared to those from CTA or MRA on a later stage in time. In practice, this limitation is almost impossible to overcome, but during the time between both investigations, the situation potentially may have changed which could influence the calculated relationship between both techniques. We have since implemented several improvements in our ongoing study protocol.

Outlook

Resources in health care are limited, and prehospital stroke projects will ultimately be assessed from a socioeconomic point of view [8,44]. If current technical problems can be solved, telemedicine might offer a rapid transfer of stroke expertise to EMS [45].

In Germany, TCCS has already been successfully performed by medical technicians under the supervision of a neurologist. Provided specific stroke training, paramedics may be able, in the future, to perform TCCS and transfer these data to a vascular neurologist for interpretation. Mikulik et al. [38] showed in a pilot study that an inexperienced health-care provider (for example paramedics) could perform a bedside examination guided by an experienced neurosonographer via telemedicine. The use of a combined neurological TCCS examination may also be extended to situations in which helicopter emergency transport is necessary, a form of transport already shown to provide the highest rates of thrombolysis in stroke patients in an Austrian study [46].

The TEMPiS project has shown to deliver high experienced stroke therapy to underserved areas and proved cost-effectiveness in hospital settings [47]. A consequent continuation of our project would be to transfer clinical and ultrasound data, obtained by regular emergency personal during the prehospital examination, to experienced stroke neurologists. The use of probability algorithms for a stroke diagnosis combined with the neurovascular status of the patient may lead to high-quality telemedical interactions between paramedics and emergency physicians on the one hand and specialists at stroke units on the other [39,42,47,48].

Conclusions

Our study demonstrates the feasibility and high diagnostic accuracy of emergency neurological examinations that include the use of mobile transcranial ultrasound systems to assess the cerebral circulation. At this point, the accuracy of stroke diagnosis is dependent on the expertise of stroke neurologists, including their ability to perform TCCS in a variety of situations and to correlate the results to patients' neurological symptoms. However, with telemedical support, administration of UCA, and specific stroke training for paramedics, this system may be feasible for broad application, including rural areas where the choice of treatment may currently be more limited due to long prehospital delays.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

MH performed data analysis and drafted the manuscript; SB acquired clinical data, participated in the study design and drafted and corrected the manuscript; TH participated in the study design and corrected the manuscript; ME acquired clinical data; MZ participated in the study design; KPI participated in the study design; JP contributed clinical data and was involved in logistics; HP contributed clinical data as clinical collaborator; UB corrected the manuscript and was involved in the study design; FS acquired clinical data, participated in the study design and drafted and corrected the manuscript. All authors read and approved the final manuscript.

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Disclosure

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Transcranial Ultrasound from Diagnosis to Early Stroke Treatment – Part 2: Prehospital Neurosonography in Patients with Acute Stroke – The Regensburg Stroke Mobile Project

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Key Words

Prehospital management of stroke · Mobile transcranial color-coded sonography · Acute stroke diagnosis · Sonothrombolysis

Abstract

Background and Purpose: The primary aim of this study was to investigate the diagnostic accuracy and time frames for neurological and transcranial color-coded sonography (TCCS) assessments in a prehospital '911' emergency stroke situation by using portable duplex ultrasound devices to visualize the bilateral middle cerebral arteries (MCAs). ***Methods:*** This study was conducted between May 2010 and January 2011. Patients who had sustained strokes in the city of Regensburg and the surrounding area in Bavaria, Germany, were enrolled in the study. After a '911 stroke code' call had been dispatched, stroke neurologists with expertise in ultrasonography rendezvoused with the paramedic team at the site of the emergency. After a brief neurological assessment had been completed, the patients underwent TCCS with optional administration of an ultrasound contrast agent in cases of insufficient temporal bone windows or if the agent had acute therapeutic relevance. The ultrasound studies were performed at the site of the emergency or in the ambulance during patient transport to the admitting hospital. Relevant timelines, such as the time from the stroke alarm to patient arrival at the hospital and the duration of the TCCS, were documented, and positive and negative predictive values for the diagnosis of major MCA occlusion were assessed. ***Results:*** A total of 113 patients were enrolled in the study. MCA occlusion was diagnosed in 10 patients. In 9 of these 10 patients, MCA occlusion could be visualized using contrast-enhanced or non-contrast-enhanced TCCS during patient transport and was later confirmed using computed tomography or magnetic resonance angiography. One MCA occlusion was missed by TCCS and 1 atypical hemorrhage was misdiagnosed. Overall, the sensitivity of a 'field diagnosis' of MCA occlusion was 90% [95% confidence interval (CI) 55.5–99.75%] and the specificity was 98% (95% CI 92.89–99.97%). The positive predictive value was 90% (95% CI 55.5–99.75%) and the negative predictive value was 98% (95% CI 92.89–

F.S. and M.H. contributed equally to this study.

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99.97%). The mean time (standard deviation) from ambulance dispatch to arrival at the patient was 12.3 min (7.09); the mean time for the TCCS examination was 5.6 min (2.2); and the overall mean transport time to the hospital was 53 min (18). ***Conclusion:*** Prehospital diagnosis of MCA occlusion in stroke patients is feasible using portable duplex ultrasonography with or without administration of a microbubble contrast agent. Prehospital neurological as well as transcranial vascular assessments during patient transport can be performed by a trained neurologist with high sensitivity and specificity, perhaps opening an additional therapeutic window for sonothrombolysis or neuroprotective strategies.

Introduction

The role of transcranial ultrasonography as a diagnostic tool is expanding to accommodate a new function as a therapeutic tool in the treatment of acute ischemic stroke. Despite the availability of treatment with intravenous recombinant tissue plasminogen activator (rtPA), now expanded to a time window of 4.5 h after stroke, only a minority of patients receive and benefit from this therapy, leaving stroke the leading cause of disability in industrialized countries. Sonothrombolysis has the potential of becoming an interesting alternative to intravenous and intra-arterial rtPA treatment in addition to a growing number of efficient thrombectomy devices in the reestablishment of cerebral blood flow following stroke [1–4]. Clinical data on sonothrombolysis in patients with acute ischemic stroke differ in efficacy and safety – the latter often due to the experimental transmission power, waveform and frequencies that are employed. Successful trials of sonothrombolysis, such as the ‘clotbust' study by Alexandrov et al. [5], demonstrated that continuous insonation using diagnostic transcranial Doppler sonography (TCD) significantly decreased the thrombus burden and the time to recanalization whereas the ‘trumbi' trial resulted in a high number of symptomatic intracerebral hemorrhages (ICHs); however, sonothrombolysis was often performed in combination with intravenous rtPA treatment [5–7]. Despite the overall excitement about ultrasound-enhanced thrombolysis in stroke, all current therapeutic approaches require the patient's hospitalization. Time, however, is the most limiting factor for all stroke treatment options and the most significant prehospital delay still occurs before the emergency dispatch center is informed, and educational campaigns often fail to increase stroke awareness [8, 9]. Given a neuron death rate of 1.9 million per minute, a treatment option that could be made available at the site of the emergency or during patient transport to the hospital could potentially lead to a paradigm shift in stroke treatment [10].

Portable color-coded duplex ultrasound machines enable clinicians to perform prehospital sonothrombolysis much earlier than treatment with intravenous rtPA, which mandatorily requires neuroimaging with cerebral computed tomography (CT) or magnetic resonance imaging (MRI) to exclude the possibility of cerebral hemorrhage. In a preliminary study, we demonstrated the feasibility of transcranial color-coded sonography (TCCS) in a nonselective, nonstroke patient series during patient transport in emergency helicopters and ambulances [11].

In 2008, a joint program for prehospital stroke diagnosis and treatment was established between the University of California, San Diego (UCSD) in the USA, and the University of Regensburg in Germany. At the UCSD Brain Ultrasound Research Laboratory (under the direction of Thilo Hölscher, MD) sonothrombolysis research is currently being performed using diagnostic ultrasound and microbubbles; in Regensburg (under the direction of Felix Schlachetzki, MD, and Sandra Boy, MD) the clinical, diagnostic part of the project is under way. After the feasibility of prehospital transcranial duplex ultrasonography had been demonstrated during the initial phase of this project, the purpose of the current study became to test the sensitivity and specificity of the treatment in patients suffering acute stroke. In this study, only ‘code stroke' patients were enrolled, and a combined neurological and TCCS examination was performed either at the patient's residence or during transport to the admitting stroke unit.

The overall aim of this study was to perform prehospital neurosonography to verify a neurological diagnosis of large intracranial vessel occlusion at the earliest possible time point. Specifically, we addressed the following points: feasibility of TCCS in prehospital diagnostics of acute stroke syndromes and determination of time frames for potential prehospital sonothrombolysis.

Materials and Methods

Population and Study Protocol

The study protocol was approved by the local ethics committee at the University of Regensburg in accordance with the Declaration of Helsinki and after review of clinical and safety data from the previous study. Patient enrollment took place during regular work hours (8 a.m.–4:30 p.m.), Monday through Friday. Despite the noninvasive diagnostic nature of the study, we requested and

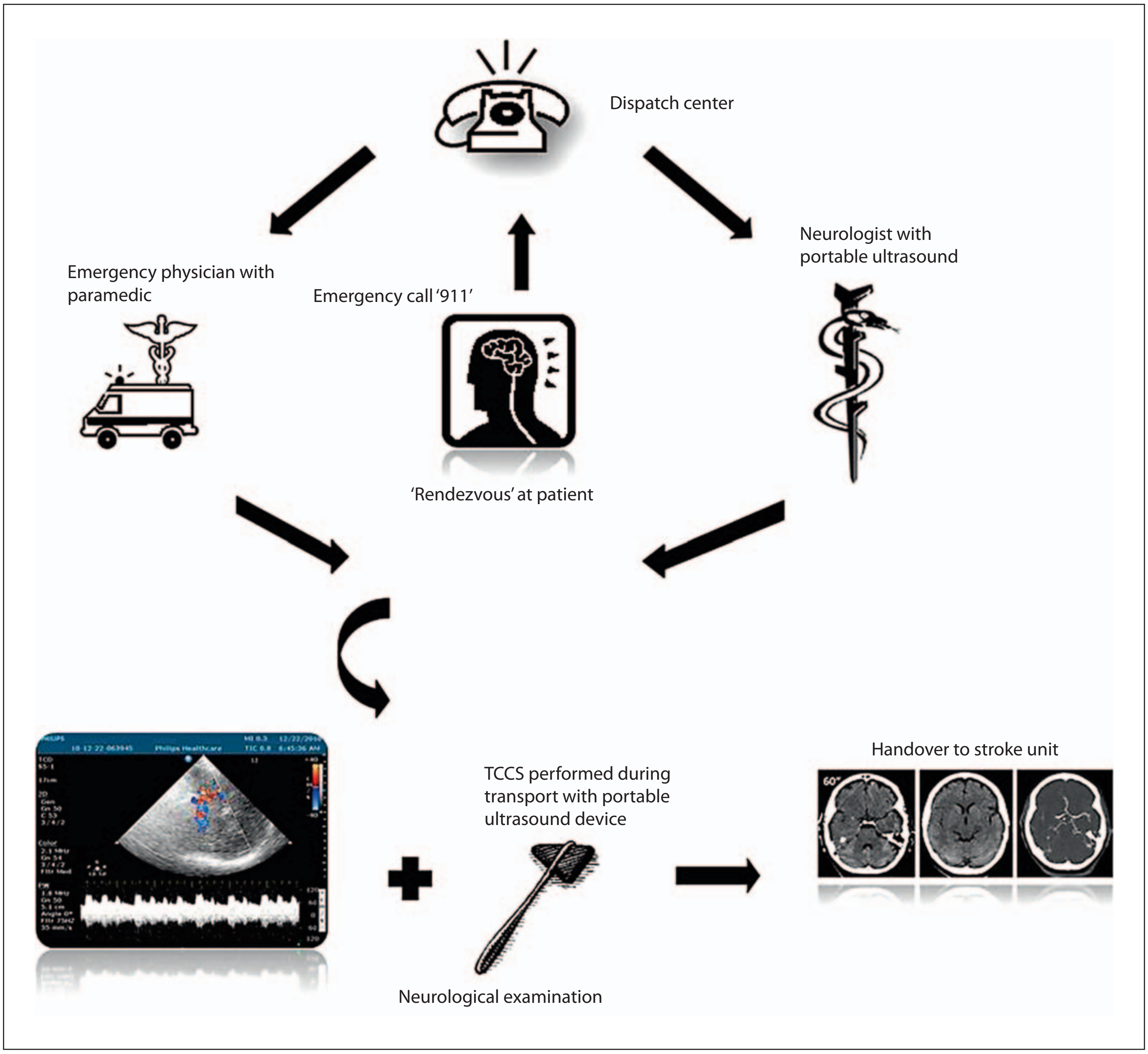


Fig. 1. Work flow of the rendezvous system, in which the emergency physician and the neurologist equipped with a portable color duplex ultrasound system converge at the side of the stroke patient and the patient is transported to the nearest hospital with a stroke unit.

received informed consent from the patient or the next available relative at the site of the emergency situation. Since the aim of the study was to show the feasibility of the procedure in emergency stroke situations, all patients with a clinical-neurological stroke diagnosis or stroke differential diagnosis were studied consecutively, independent of the severity of the patient's symptoms. A rendezvous protocol was used to treat the patient. After a 112 stroke call was made (equivalent to a 911 call in the USA), the ambulance team (emergency physician and paramedic) and the stroke team [an experienced neurologist and a paramedic driver in a dedicated 'stroke mobile' (BMW, series 1)] rendezvoused at the site of the incident (fig. 1). The protocol required, without exception, first aid and stabilization of the patient's vital parameters, even in cases in which the neurosonography team arrived before the emergency physician. Then a brief neurological examination was made, followed immediately by a TCCS assessment.

The ultrasound study took place either at the site of the initial treatment (patient's couch or bed) or during ambulance transport to the nearest stroke unit (table 1). The various positioning of the patient in the different settings, e.g. sitting, lying, investigator in front or back of patient, and the sometimes bumpy ride within the ambulance car demanded a high experience and flexibility of the investigator.

Ultrasound Equipment and Data Acquisition

Two portable color duplex ultrasound machines equipped with a phased-array transducer capable of transcranial imaging were used: SonoSite Micromaxx with a P17 transducer (SonoSite Inc., Bothell, Wash., USA) and Philips CX50 with a P2–5 transducer (Philips Ultrasound, Bothell, Wash., USA). We used the standard setting with a transmission frequency of 2 Hz for brightness, color and Doppler mode on both machines. Images were stored as bitmap (Micromaxx®) and DICOM (CX50®) files on the hard drive and converted later to jpg files for data transfer and off-line analysis.

Optional use of an ultrasound contrast agent (SonoVue®, Bracco Imaging SpA, Milan, Italy) allowed us to increase our diagnostic confidence in cases of inferior transcranial bone windows and to save examination time [12]; it also proved valuable during examinations made difficult during emergency transport. Intravenous injections of 0.5–2 ml contrast agent were administered, depending on the quality of the temporal bone window as previously described [13]. After identification of the best temporal bone window, the protocol requested visualization in color mode and confirmatory flow measurements in both middle cerebral arteries (MCAs) in the proximal M1 segment on both sides. After MCA visualization using color Doppler mode, flow measurements were performed in the proximal MCA (M1) segment using spectral Doppler sonography. Angle correction was not performed. The examiner could decide whether to extend the protocol to measurements in the anterior cerebral (ACA) and posterior cerebral (PCA) arteries. Proximal MCA occlusions were diagnosed when the ipsilateral ACA and/or contralateral ACA and MCA could be visualized, confirming the existence of a sufficient temporal bone window with or without echocontrast agents. Distal MCA or MCA branch occlusions were defined according to the criteria published by Zanette et al. [14]. The TCCS examination time was defined as the time from the first to the last image, as documented in the image files.

A simplified data collection sheet was used, in which we noted several items: the timing of our response to the emergency call, arrival at the patient's side, and beginning and end of the ultrasound examination; the final diagnosis after the patient's discharge from the hospital; the stroke treatment that was used; and whether visualization of both MCAs had been achieved. Data derived from neurovascular investigations such as CT angiography (CTA), MR angiography (CTA), or in-house neurosonography were collected and correlated to the results of the prehospital TCCS.

Statistical Analysis

Based on the data collected, we calculated the sensitivity, specificity, and positive and negative predictive values, as well as the respective 95% CIs, of the procedure in determining occlusion of the MCA. All data were entered into an Excel worksheet and calculated using StatXact®9 (http://www.cytel.com).

Table 1. Study demographics

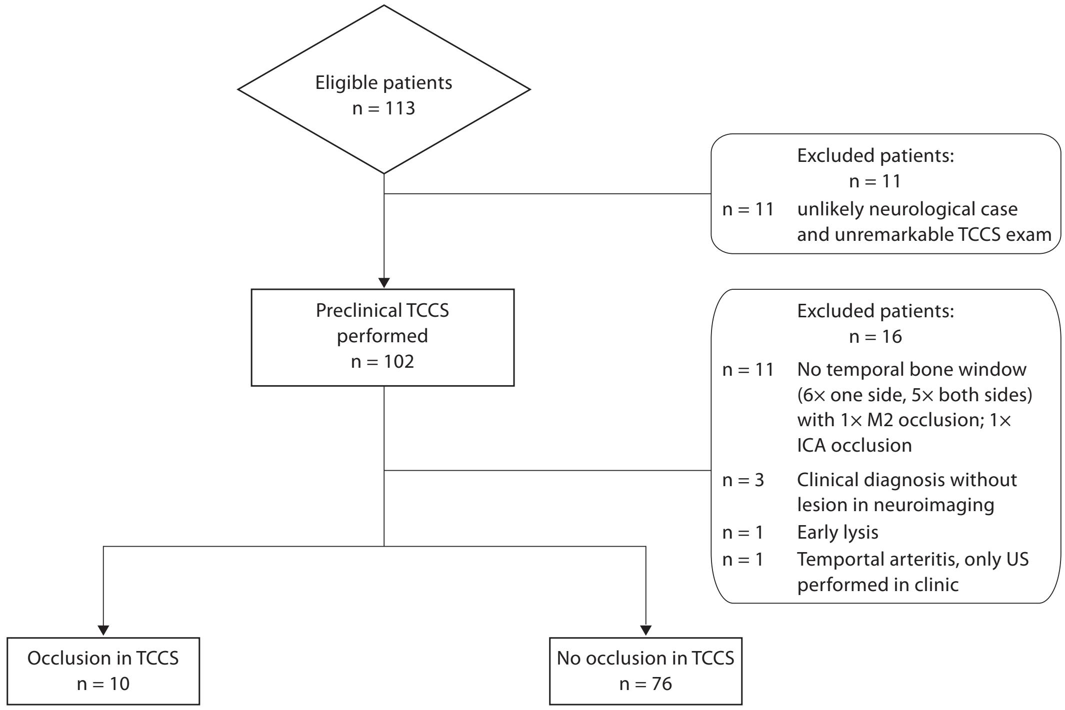
Total patients, n	113
Stayed at home (no stroke, ultrasound examination unremarkable), n	11
Clinic admission, n	102
Mean age in years, SD	80.6 ± 13.52
Sex, w/m	63/50
Site of ultrasound examination	
Patient's home	56 (50%)
Ambulance during patient transport	49 (43%)
Private office practice	4 (4%)
Public space	2 (2%)
Senior citizen home	2 (2%)
Stroke neurologist examinations, n	
S.B.	61
F.S.	49
M.E.	3
Time from dispatch to arrival at patient in min, SD	12.3 ± 7.09
Time from arrival at patient to handover of patient to hospital, mean ± SD, min	53 ± 18
Ultrasound examination time, mean ± SD, min	5.6 ± 2.2
Contrast-enhanced TCCS, n	41 (36%)
Stroke[1] diagnosis at hospital discharge, n	73
Intravenous thrombolysis, n	
Yes	9
No due to exclusion criteria	72
Thrombectomy	1
M1–MCA occlusion, n	10 (9%)

SD = Standard deviation; S.B. = Sandra Boy; F.S. = Felix Schlachetzki; M.E. = Michael Ertl.

[1] Stroke = TIA, ischemic stroke, or hemorrhagic stroke.

Results

During the 9-month clinical period, we used TCCS to examine 113 patients for acute ischemic stroke symptoms (fig. 2). The mean time from the stroke code dispatch to arrival at the patient's side was 11 min. The examinations were performed by board-certified stroke neurologists (S.B. examined 61 patients and F.S. 49 patients) and a senior resident with certification for neurosonography by the German Society for Ultrasound in Medicine (M.E. examined 3 patients). The patients' mean age in this study was 80.6 years (SD 13.52 years) and 56% of the patients were female. TCCS was performed to screen for major vessel occlusion in cases in which the symptoms were unequivocally due to stroke, as a confirmatory investigation in cases of suspected stroke, or for additional exclusion in cases in which the diagnosis was a disease mimicking stroke or another internal medicine



MCA-M1 occlusion		Standard stroke imaging*		
		occlusion	no occlusion	total
Preclinical TCCS	occlusion	9	1**	10
	no occlusion	1***	75	76
	total	10	76	86

* CTA, MRA, and CCT according to diagnostic pathway in stroke unit.
** Massif ICH described as distal MCA occlusion.
*** Contrast through filter; PCA described instead of MCA occlusion.

Diagnostic accuracy

Artery	Se (95% CI)	Sp (95% CI)	PPW (95% CI)	NPW (95% CI)
M1	90% (55.55–99.75)	98% (92.89–99.97)	90% (55.55–99.75)	98% (92.89–99.97)

Se = Sensitivity; Sp = specificity; PPW = positive predictive value; NPW = negative predictive value

Fig. 2. Flow diagram showing the imaging pathway in diagnosing ischemic stroke. A 2 × 2 table showing the calculated diagnostic accuracy.

diagnosis. As expected, 11 (10%) of 113 patients did not have a suitable temporal bone window; however, we did not administer an ultrasound contrast agent (UCA) if the patient's neurological symptoms were unlikely to be due to stroke. The average time taken to perform TCCS was 5.6 min (table 1). A UCA was used in 41 (36%) of 113 cases to improve our confidence in the diagnosis or to save time.

The mean time from arrival at the patient's side to delivery of the patient to the nearest clinic with a stroke unit

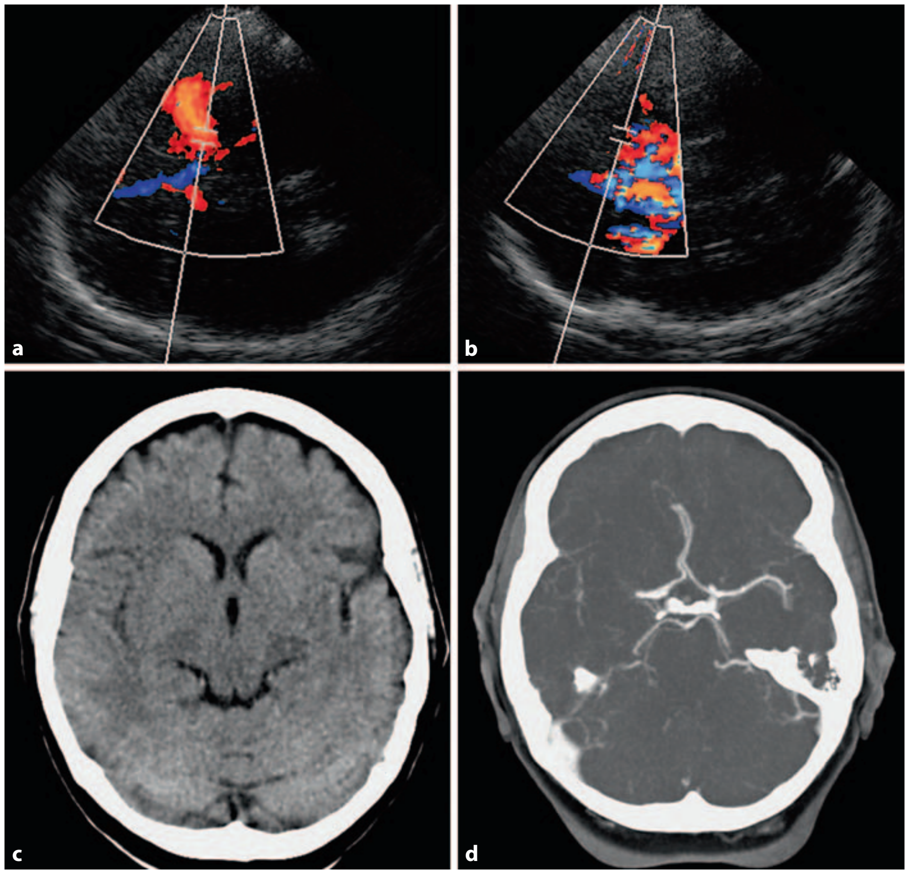


Fig. 3. Images obtained in a 57-year-old patient with acute left-sided hemiparesis and right-sided gaze. **a**, **b** Contrast-enhanced TCCS images showing a patent left MCA 25 min after symptom onset (**a**) and proximal occlusion of the right MCA (**b**), which is consistent with the patient's stroke symptoms. **c** Cerebral CT scan obtained 65 min after symptom onset exhibiting mild hypointensities of the right basal ganglia. **d** CTA confirming right MCA occlusion. (To compare to panel **b**, rotate 90° counterclockwise.)

(Department of Neurology of the University of Regensburg, Bezirksklinikum Regensburg, or Department of Neurology, Krankenhaus der Barmherzigen Brüder Regensburg, Regensburg) was 53 min (SD 18 min).

Overall, 9 of 10 MCA occlusions were correctly identified by prehospital TCCS (fig. 3). In 1 patient, a PCA was mistaken for a patent MCA when the UCA was incorrectly injected through a filter system, resulting in the destruction of the microbubbles and inferior image quality in the early days of the study. Also, TCCS resulted in misdiagnosis of a distal MCA mainstem occlusion according to the Zanette index (fig. 4) [14]. In this patient, an atypical parietooccipital ICH caused dislocation of the MCA, which led to a near-perpendicular angle of insonation. Retrospectively, attention to the lack of resistance in the low-flow profile and the use of UCA may have helped to avoid the misdiagnosis. Patent MCAs, as demonstrated by standard neurovascular imaging (CTA, MRA or neurosonography) in the hospital, were diagnosed correctly in 75 of 76 cases. In 1 patient, in whom an additional atypical frontal ICH caused severe left-sided hemiparesis, a clinical syndrome potentially attributed to MCA occlusion, normal flow in the MCA was observed and confirmed by CTA. In 2 additional patients with space-occupying subdural hematomas, unremarkable flow was also observed in both MCAs.

We calculated the sensitivity, specificity, positive predictive and negative predictive values in achieving a correct diagnosis of MCA occlusion. Our findings are as follows: sensitivity 90% (95% CI 55.5–99.75%); specificity 98% (95% CI 92.89–99.97%); positive predictive value 90% (95% CI 55.5–99.75%), and negative predictive value 98% (95% CI 92.89–99.97%).

Discussion

We were able to demonstrate that a reliable diagnosis of MCA occlusion can be made using a portable duplex ultrasound device in the prehospital setting – either at the site of the emergency or during patient transport. The added use of contrast agent microbubbles was ben-

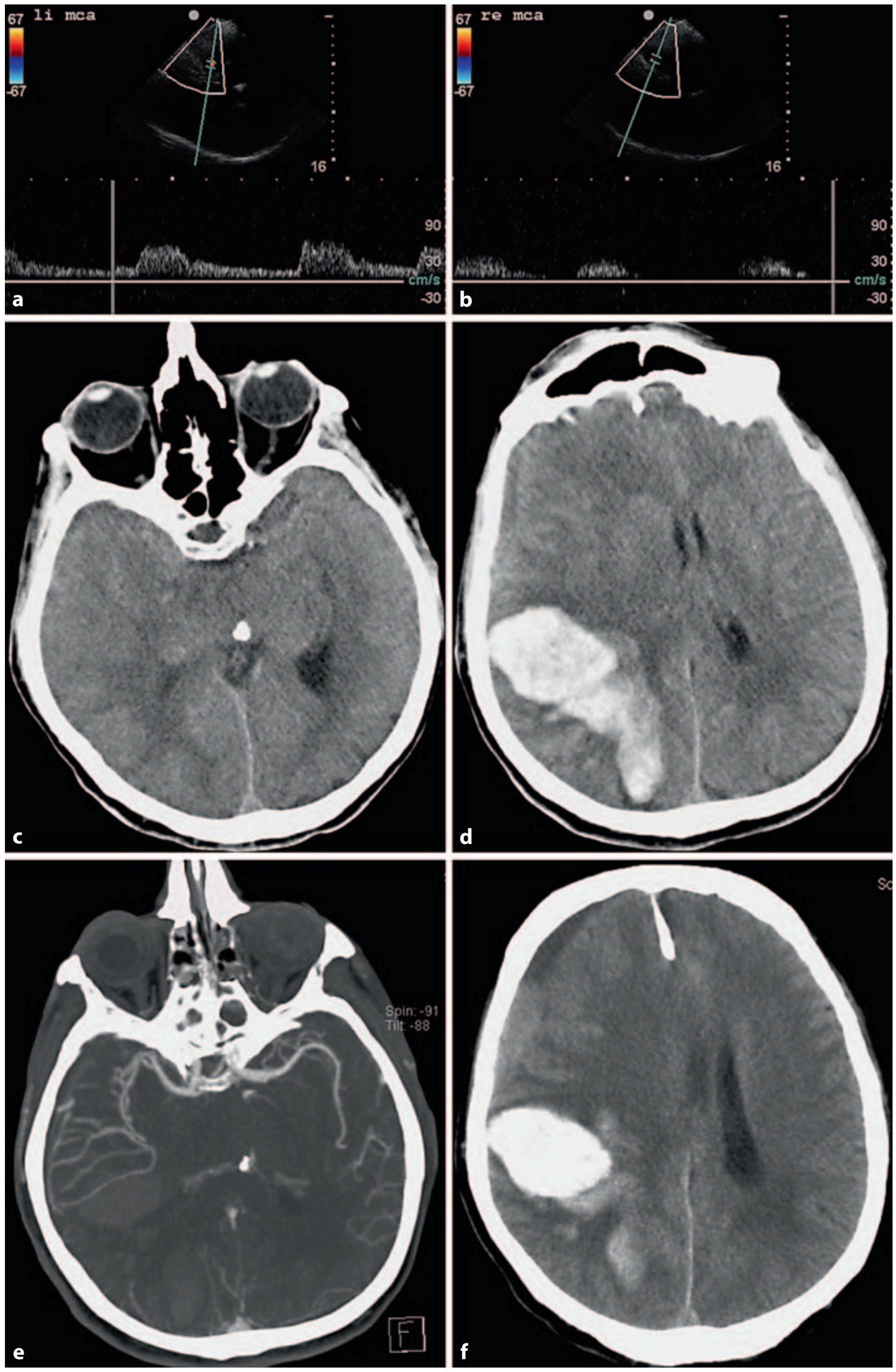


Fig. 4. Images obtained in an 80-year-old patient with acute left-sided hemiparesis and neglect. **a**, **b** Unenhanced TCCS images obtained 30 min after symptom onset showing a patent left MCA and significant flow reduction in the right MCA, which was interpreted to be consistent with distal MCA occlusion (according to Zanette), but without a high-resistance flow pattern. **c**, **d** Unenhanced cerebral CT scans obtained 60 min later, showing a midline shift at the level of the circle of Willis (**c**) and a large right-sided parietooccipital atypical ICH with a small-convexity subdural hematoma (**d**). **e**, **f** After intubation and before neurosurgical evacuation, CTA revealed severe dislocation of the right MCA, leading to a near-perpendicular angle of insonation for TCCS; this was also reflected in the absent high-resistance flow pattern, which would be expected in cases of distal MCA occlusions.

eficial when there was an insufficient temporal bone window, to save examination time, to increase diagnostic confidence, or during difficult examinations. Supporting the clinical diagnoses of hemispheric brain ischemia at the earliest possible time point could potentially open new avenues for image-guided transcranial sonothrombolysis in patients suffering acute stroke while still 'in the field'.

Ischemic stroke therapy is time critical and hence to decrease the time from symptom onset to initiation of intravenous thrombolysis, minimum diagnostic prerequisites were established [10, 15]. Mobile color-coded Duplex ultrasound systems now have image qualities high enough to perform neurovascular ultrasonography even in difficult imaging situations [11]. Given average patient transport times ranging from 30 to 65 min from arrival at the patient's side to patient delivery to the nearest hospital, as analyzed by Teuschl and Brainin [8] in their recent meta-analysis, prehospital TCCS may fill both a diagnostic and a potential therapeutic gap. A single case report has been published to date in which prehospitalization TCCS aided the clinical diagnosis of left-sided hemispheric stroke [16].

Sonothrombolysis has emerged as a new potential tool for stroke therapy in combination with administration of rtPA or ultrasound microbubbles. Ultrasound microbubbles are of special interest because they could replace thrombolytic agents in the treatment of stroke and can be applied 'in the field'. Basic mechanisms of sonothrombolysis that are being investigated in this regard include, among others, microstreaming derived from ultrasound contrast agent destruction and stable cavitation [17]. Although experimental low-frequency, high-intensity ultrasound systems displayed greater thrombolytic potential in experimental studies, their application to human stroke has produced negative results, including symptomatic ICH to some extent [6, 18]. Other studies, however, in which TCD ultrasound with and without contrast agents provided faster relief of an intra-arterial clot burden, leading to faster recanalization in experimental and clinical studies [5, 7, 10, 19, 20].

Symptomatic ICH is a serious differential diagnosis for ischemic stroke. In this study, we only had 2 cases of ICH. Both ICHs were not visualized because prehospital TCCS was not performed to exclude hemorrhage but to primarily detect a major MCA occlusion. In one of these cases, displacement of the MCA led to a false diagnosis of distal MCA occlusion. This misdiagnosis could have been avoided if we had taken into account the Zanette index as well as the missing high-resistance flow pattern associated with distal occlusion. The other patient, a case of atypical frontal ICH, had an unremarkable flow profile in the MCA . The only scenario in which ICH would lead to MCA occlusion would be a massive space-occupying hemorrhage along with a high Glasgow Coma Scale score. In other words, MCA occlusions are a highly unexpected finding in patients suffering from typical hypertensive basal ganglia ICHs. Two additional patients had symptomatic space-occupying subdural hematomas, which caused stroke-like symptoms, and an unremarkable MCA flow. Overall, the incidence of ICH was lower than expected in our study compared with general statistics, i.e. those published in the Interstroke Study [21].

Little is known about the effect of contrast-enhanced TCCS on the ICH itself. To date, diagnostic ce-TCCS has been extremely safe, and there have been no published reports of related ICH or related blood-brain barrier opening in rabbits and humans, which represents a lesser form of neurovascular compromise [22–24]. Although some risk may exist, ultrasound spatial peak–temporal peak intensities, as well as rarefactional pressure values, are significantly attenuated by the temporal bone, and the mechanical effects of the microbubble response are limited to the intravascular compartment. Stroick et al. [25] performed a study using a rat model of ICH in which they injected collagenase intracerebrally to produce a basal ganglia hemorrhage. This elegant study in which ce-TCCS was performed with a 50-mm spacer between transducer and skull to account for differences in the beam did not lead to greater hemorrhage volumes, edema or clinical deterioration in rats.

The 'stroke mobile' concept applied in this study did not lead to any delay in prehospital management after the patient's arrival until handover in the hospital (mean time 65 ± 25 min) since the neurological and ultrasound investigation was performed either during transport or before the stretcher arrived. Duration of patient transport was comparable to previously published data [8, 26]. Half of the TCCS examinations were performed at the primary site of the stroke incident and most were finished before the first-aid personnel arrived with the stretcher. We performed 49 (43%) of the 113 investigations during transport in the ambulance; these cases were sometimes challenging and often led to administration of UCA for diagnostic confidence and reduced time. Other strategies of prehospital stroke imaging and treatment include the use of mobile CT scanners with telemedicine support, presence of a neurologist, technicians, and access to clinical chemistry, which are all represented in the 'Mobile Stroke Unit', available in Homburg since 2008, and the 'STEMO – Stroke Emergency Mobile', available in Berlin since 2011 [27]. The only 2 cases published so far had a dispatch-to-decision time of 35 min, which is shorter than the average dispatch-to-needle time in conventional stroke unit scenarios. Prehospital neurosonography in cases of proven MCA occlusion with corresponding neurological symptoms as shown in figure 2 may become more frequent with increasing experience of physicians and ultrasonography-trained paramedics.

In summary, this first large study on prehospital neurosonography with neurological expertise in acute stroke therapy demonstrates the high sensitivity and specificity of TCCS examinations 'in the field' in detecting thrombotic conditions – mainly MCA occlusions. The ultrasound investigation should be performed by a well-trained and experienced investigator and interpreted only in the context of the neurological symptoms. This study forms the basis on which further refinements and standardizations of prehospital neurosonography and neurological stroke assessment can be made. Ultimately, patient transport to the nearest stroke unit provides a relevant time window for sonothrombolyis in acute MCA occlusion.

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