Cerebrovascular Diseases

Original Paper

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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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–

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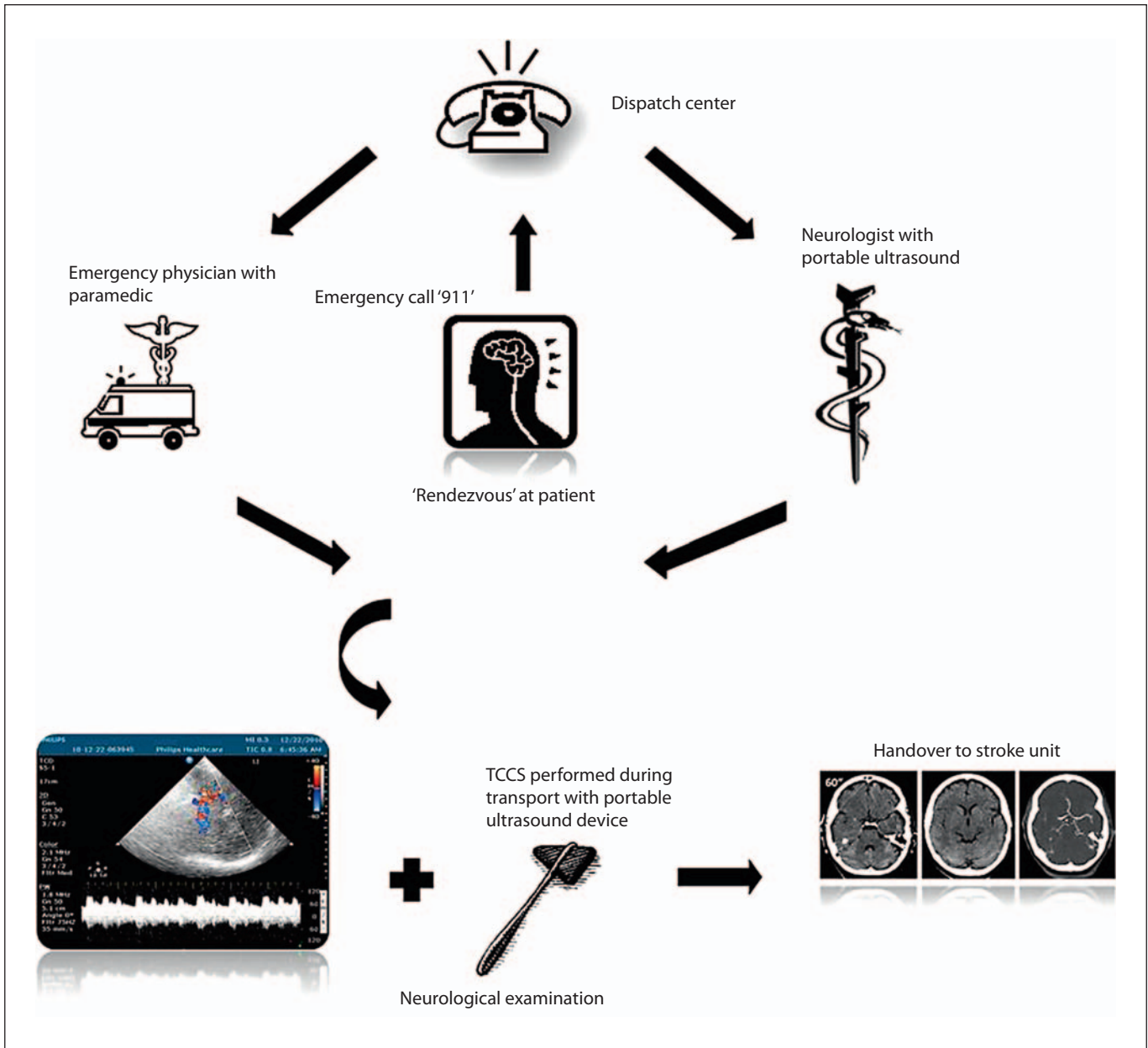
Fig. 1. Work flow of the rendezvous system, in which the emergency physician and the neurologist equipped with a portable color duplex ultrasound system converge at the side of the stroke patient and the patient is transported to the nearest hospital with a stroke unit.

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.

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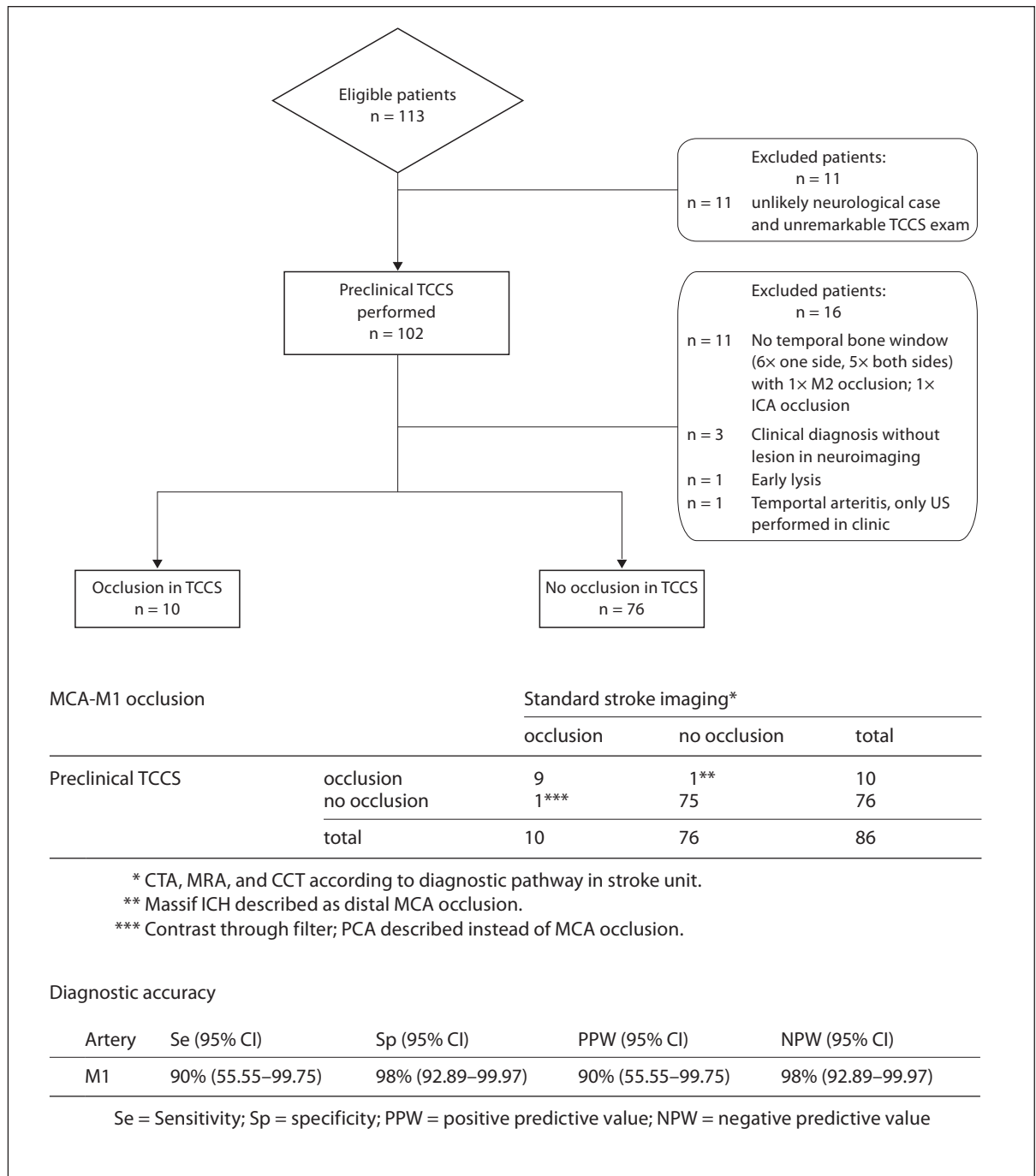
Fig. 2. Flow diagram showing the imaging pathway in diagnosing ischemic stroke. A 2 × 2 table showing the calculated diagnostic accuracy.

The figure contains the following content:

Eligible patients n = 113

Excluded patients: n = 11
n = 11 unlikely neurological case and unremarkable TCCS exam

Preclinical TCCS performed n = 102

Excluded patients: n = 16
n = 11 No temporal bone window (6× one side, 5× both sides) with 1× M2 occlusion; 1× ICA occlusion
n = 3 Clinical diagnosis without lesion in neuroimaging
n = 1 Early lysis
n = 1 Temportal arteritis, only US performed in clinic

Occlusion in TCCS n = 10

No occlusion in TCCS n = 76

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

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
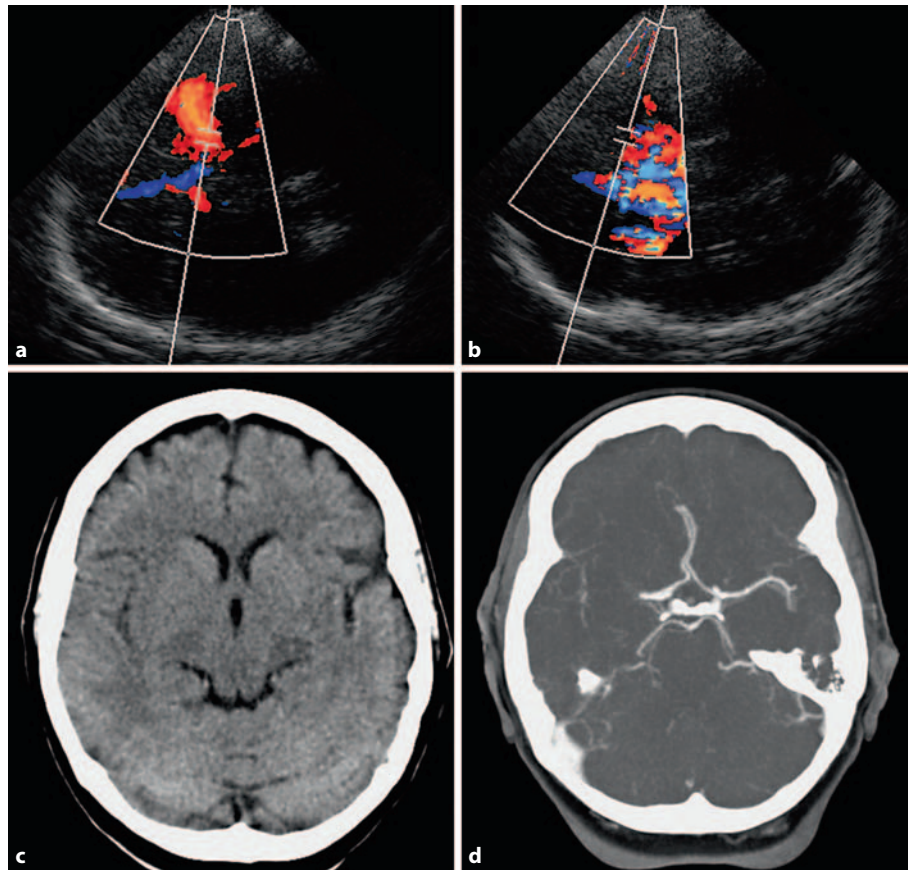
Fig. 3. Images obtained in a 57-year-old patient with acute left-sided hemiparesis and right-sided gaze. **a**, **b** Contrast-enhanced TCCS images showing a patent left MCA 25 min after symptom onset (**a**) and proximal occlusion of the right MCA (**b**), which is consistent with the patient's stroke 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-
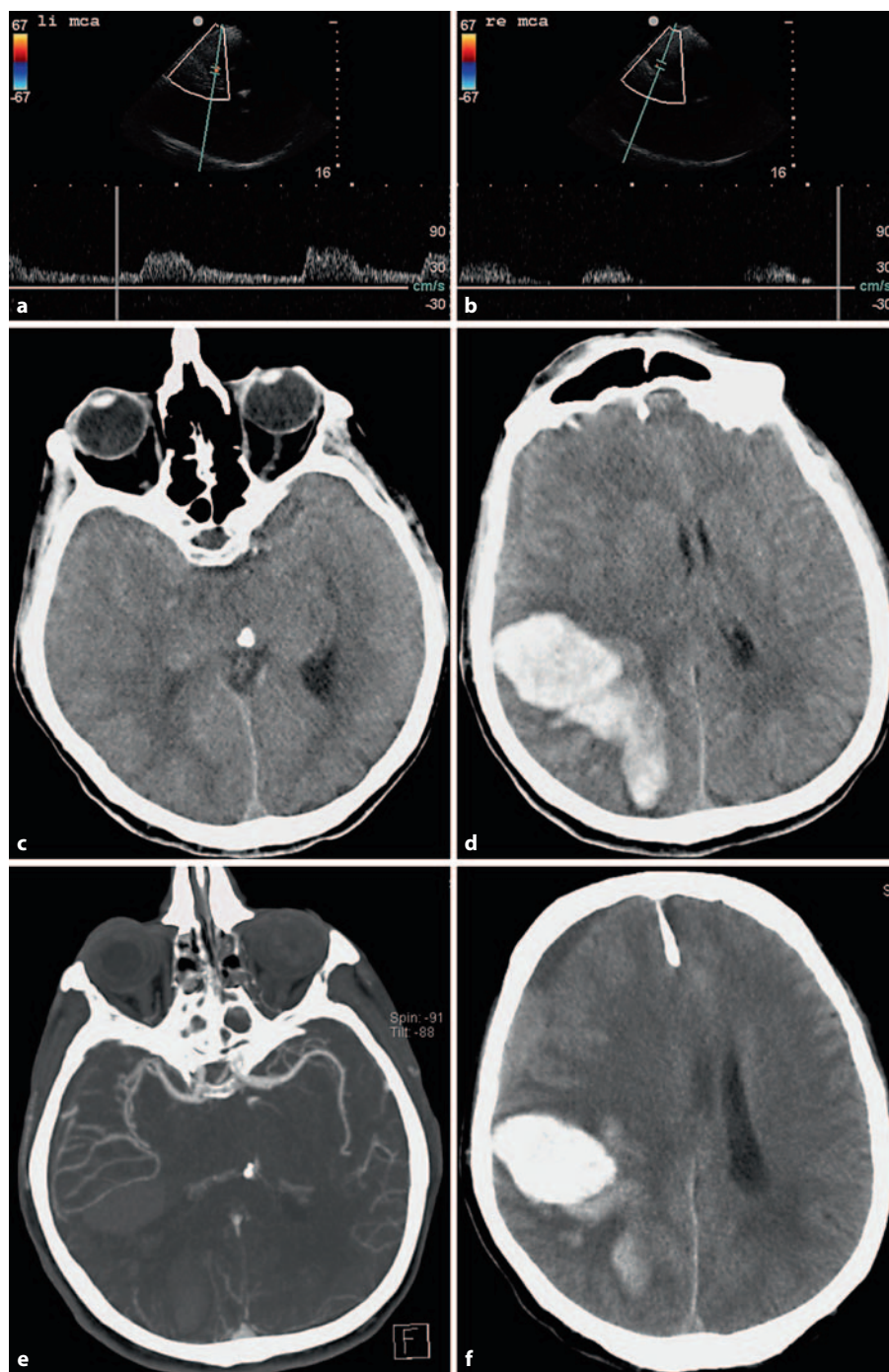
Fig. 4. Images obtained in an 80-year-old patient with acute left-sided hemiparesis and neglect. **a**, **b** Unenhanced TCCS images obtained 30 min after symptom onset showing a patent left MCA and significant flow reduction in the right MCA, which was interpreted to be consistent with distal MCA occlusion (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 Du-

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plex 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.

Acknowledgments

References

1 Meairs S, Culp W: Microbubbles for thrombolysis of acute ischemic stroke. Cerebrovasc Dis 2009;27(suppl 2):55–65.

2 del Zoppo GJ, Higashida RT, Furlan AJ, Pessin MS, Rowley HA, Gent M: Proact: A phase II randomized trial of recombinant pro-urokinase by direct arterial delivery in acute middle cerebral artery stroke. PROACT investigators. Prolyse in acute cerebral thromboembolism. Stroke 1998;29:4–11.

3 Costalat V, Machi P, Lobotesis K, Maldonado I, Vendrell JF, Riquelme C, Mourand I, Milhaud D, Heroum C, Perrigault PF, Arquizan C, Bonafe A: Rescue, combined, and standalone thrombectomy in the management of large vessel occlusion stroke using the Solitaire device: a prospective 50-patient single-center study: timing, safety, and efficacy. Stroke 2011;42:1929–1935.

4 Roth C, Mielke A, Siekmann R, Ferbert A: First experiences with a new device for mechanical thrombectomy in acute basilar artery occlusion. Cerebrovasc Dis 2011;32:28–34.

5 Alexandrov AV, Molina CA, Grotta JC, Garami Z, Ford SR, Alvarez-Sabin J, Montaner J, Saqqur M, Demchuk AM, Moye LA, Hill MD, Wojner AW: Ultrasound-enhanced systemic thrombolysis for acute ischemic stroke. N Engl J Med 2004;351:2170–2178.

6 Daffertshofer M, Gass A, Ringleb P, Sitzer M, Sliwka U, Els T, Sedlaczek O, Koroshetz WJ, Hennerici MG: Transcranial low-frequency ultrasound-mediated thrombolysis in brain ischemia: increased risk of hemorrhage with combined ultrasound and tissue plasminogen activator: Results of a phase II clinical trial. Stroke 2005;36:1441–1446.

7 Tsivgoulis G, Eggers J, Ribo M, Perren F, Saqqur M, Rubiera M, Sergentanis TN, Vadikolias K, Larrue V, Molina CA, Alexandrov AV: Safety and efficacy of ultrasound-enhanced thrombolysis: a comprehensive review and meta-analysis of randomized and nonrandomized studies. Stroke 2010;41:280–287.

8 Teuschl Y, Brainin M: Stroke education: Discrepancies among factors influencing prehospital delay and stroke knowledge. Int J Stroke 2010;5:187–208.

9 Mikulik R, Goldemund D, Reif M, Brichta J, Neumann J, Jarkovsky J, Kryza J: Calling 911 in response to stroke: no change following a four-year educational campaign. Cerebrovasc Dis 2011;32:342–348.

10 Saver JL: Time is brain-quantified. Stroke 2006;37:263–266.

11 Holscher T, Schlachetzki F, Zimmermann M, Jakob W, Ittner KP, Haslberger J, Bogdahn U, Boy S: Transcranial ultrasound from diagnosis to early stroke treatment. 1. Feasibility of prehospital cerebrovascular assessment. Cerebrovasc Dis 2008;26:659–663.

12 Seidel G, Meairs S: Ultrasound contrast agents in ischemic stroke. Cerebrovasc Dis 2009;27(suppl 2):25–39.

13 Sauerbruch S, Schlachetzki F, Bogdahn U, Valakiene J, Holscher T, Harrer JU: Application of transcranial color-coded duplex sonography in stroke diagnosis. Curr Med Imaging Rev 2009;5:39–54.

14 Zanette EM, Fieschi C, Bozzao L, Roberti C, Toni D, Argentino C, Lenzi GL: Comparison of cerebral angiography and transcranial Doppler sonography in acute stroke. Stroke 1989;20:899–903.

15 The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group: Tissue plasminogen activator for acute ischemic stroke. . N Engl J Med 1995;14:1581–1587.

16 Wilson MH, Levett DZ, Dhillon S, Mitchell K, Morgan J, Grocott MP, Imray C: Stroke at high altitude diagnosed in the field using portable ultrasound. Wilderness Environ Med 2011;22:54–57.

17 Collis J, Manasseh R, Liovic P, Tho P, Ooi A, Petkovic-Duran K, Zhu Y: Cavitation microstreaming and stress fields created by microbubbles. Ultrasonics 2010;50:273–279.

18 Daffertshofer M, Fatar M: Therapeutic ultrasound in ischemic stroke treatment: Experimental evidence. Eur J Ultrasound 2002;16:121–130.

19 Molina CA, Ribo M, Rubiera M, Montaner J, Santamarina E, Delgado-Mederos R, Arenillas JF, Huertas R, Purroy F, Delgado P, Alvarez-Sabin J: Microbubble administration accelerates clot lysis during continuous 2-mHz ultrasound monitoring in stroke patients treated with intravenous tissue plasminogen activator. Stroke 2006;37:425–429.

20 Holscher T, Raman R, Ernstrom K, Parrish J, Le DT, Lyden PD, Mattrey RF: In vitro sonothrombolysis with duplex ultrasound: First results using a simplified model. Cerebrovasc Dis 2009;28:365–370.

21 O'Donnell MJ, Xavier D, Liu L, Zhang H, Chin SL, Rao-Melacini P, Rangarajan S, Islam S, Pais P, McQueen MJ, Mondo C, Damasceno A, Lopez-Jaramillo P, Hankey GJ, Dans AL, Yusoff K, Truelsen T, Diener HC, Sacco RL, Ryglewicz D, Czlonkowska A, Weimar C, Wang X, Yusuf S: Risk factors for ischaemic and intracerebral haemorrhagic stroke in 22 countries (the Interstroke Study): A case-control study. Lancet 2010; 376:112–123.

22 Hynynen K, McDannold N, Martin H, Jolesz FA, Vykhodtseva N: The threshold for brain damage in rabbits induced by bursts of ultrasound in the presence of an ultrasound contrast agent (Optison). Ultrasound Med Biol 2003;29:473–481.

23 Hynynen K, McDannold N, Vykhodtseva N, Jolesz FA: Non-invasive opening of BBB by focused ultrasound. Acta Neurochir Suppl 2003;86:555–558.

24 Schlachetzki F, Holscher T, Koch HJ, Draganski B, May A, Schuierer G, Bogdahn U: Observation on the integrity of the blood-brain barrier after microbubble destruction by diagnostic transcranial color-coded sonography. J Ultrasound Med 2002;21:419–429.

25 Stroick M, Alonso A, Fatar M, Griebe M, Kreisel S, Kern R, Gaud E, Arditi M, Hennerici M, Meairs S: Effects of simultaneous application of ultrasound and microbubbles on intracerebral hemorrhage in an animal model. Ultrasound Med Biol 2006;32:1377–1382.

26 Ziegler V, Rashid A, Muller-Gorchs M, Kippnich U, Hiermann E, Kogerl C, Holtmann C, Siebler M, Griewing B: Mobile computing systems in preclinical care of stroke. Results of the Stroke Angel initiative within the BMBF project PerCoMed (in German). Anaesthesist 2008;57:677–685.

27 Walter S, Kostpopoulos P, Haass A, Helwig S, Keller I, Licina T, Schlechtriemen T, Roth C, Papanagiotou P, Zimmer A, Viera J, Korner H, Schmidt K, Romann MS, Alexandrou M, Yilmaz U, Grunwald I, Kubulus D, Lesmeister M, Ziegeler S, Pattar A, Golinski M, Liu Y, Volk T, Bertsch T, Reith W, Fassbender K: Bringing the hospital to the patient: first treatment of stroke patients at the emergency site. PLoS One 2010;5:e13758.