НЕВРОСОНОЛОГИЯ
И МОЗЪЧНА
ХЕМОДИНАМИКА

*Издание на Българската асоциация
по невросонология
и мозъчна хемодинамика*

NEUROSONOLOGY
AND CEREBRAL
HEMODYNAMICS

*Official Journal of the Bulgarian Society
of Neurosonology
and Cerebral Hemodynamics*

REGIONAL TEACHING COURSE
of the European Academy of Neurology

preceded by

9th Meeting of the Bulgarian Society of Neurosonology and Cerebral Hemodynamics

October 2–5, 2014 | Sofia, Bulgaria

Programme and Lectures

YEAR OF THE BRAIN 2014 EUROPE

Том 10, Брой 2
2014

Volume 10, Number 2
2014

ГОДИНИ 10 YEARS

НЕВРОСОНОЛОГИЯ И МОЗЪЧНА ХЕМОДИНАМИКА

NEUROSONOLOGY AND CEREBRAL HEMODYNAMICS

Издание на Българската асоциация по невросонология и мозъчна хемодинамика

БАНМХ BSNCH

Official Journal of the Bulgarian Society of Neurosonology and Cerebral Hemodynamics

Том 10, 2014, Брой 2 | **Volume 10, 2014, Number 2**

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Official Journal of the Bulgarian Society of Neurosonology and Cerebral Hemodynamics

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Welcome Message

Уважаеми колеги и приятели,

Изминалата 2013 година остана в историята с големия успех, който постигнахме като организатори и домакини на 16-я Световен форум по невросонология на Световната федерация по неврология.

В настоящата 2014 година ние отбелязваме четири нови събития:

– Честване на 10-годишен юбилей на нашето списание „Невросонология и мозъчна хемодинамика";

– Организиране на Регионалния курс на обучение на Европейската академия по неврология, който се провежда отново в град София, между 2 и 5 октомври 2014 година в Парк хотел Москва;

– Провеждане на традиционната девета среща на нашето сдружение, съвместно с Българската академия на науките и изкуствата;

– Съпричастност към инициативата „Година на мозъка" на Европейския съвет по мозъка и обозначаване на всички събития на БАНМХ до края на 2015 година с Европейския знак за нея.

Водещи европейски специалисти по неврология ще представят актуални проблеми на стареещия мозък, мозъчния инсулт и деменция, нови технологии в неврорехабилитацията и невросонологията.

За участие в обучението са се регистрирали специалисти по неврология, физикална медицина, рехабилитация, кинезитерапия, студенти и специализанти от 10 държави – България, Македония, Сърбия, Русия, Молдова, Украйна, Албания, Румъния, Босна и Херцеговина и Египет.

Пожелавам Ви ползотворно участие във форума!

Ваша

Акад. проф. Е. Титянова, д.м.н.
Председател на БАНМХ

Dear Colleagues and Friends,

In the past year, 2013, the 16th World Neurosonology Meeting of the World Federation of Neurology took its rightful place in history with its immense success that we achieved as hosts and organizers.

In the current year, 2014, we define four new events:

– Celebration of the 10th anniversary of our scientific Journal "Neurosonology and Cerebral Hemodynamics";

– Planning and organization of the Regional Teaching Course of the European Academy of Neurology, which will take place in Sofia from 2nd to 5th October 2014, in Park Hotel Moskva;

– Organization of our traditional 9th Meeting of the BSNCH jointly with the Bulgarian Academy of Sciences and Arts;

– Supporting the initiative "Year of the Brain" of the European Council on Brain and designating with its logo all the BSNCH events which will be held till the end of 2015.

Leading European specialists in the field of Neurology will present current problems on the topics of the aging brain, stroke and dementia, and new technologies applied in Neurorehabilitation and Neurosonology.

For the EAN Regional Teaching Course we have registered delegates from the fields of Neurology, Physical Medicine, Rehabilitation, Physiotherapy, students and graduates in training from 10 countries – Bulgaria, Republic of Macedonia, Serbia, Russia, Moldova, Ukraine, Albania, Romania, Bosnia and Herzegovina, and Egypt.

I wish you a fruitful participation in the forum!

Sincerely,

Acad. Prof. E.Titianova, MD, PhD, DSc
President of BSNCH

Ten Years Journal

Уважаеми читатели,

През изминалите 10 години списанието "Невросонология и мозъчна хемодинамика" се утвърди като водещо периодично научно списание в областта на неврологията и невросонологията в България и породи нарастващ интерес на международната неврологична общност към него. То се издава на български и английски език и е свободно достъпно онлайн в интернет страницата на Асоциацията.

Чрез информиране на читателите за най-новите достижения в невросонологията и мозъчната хемодинамика и тяхното приложение в неврологията, неонатологията, педиатрията, съдовата хирургия и други области на медицината, списанието попълни съществуваща празнота в българската научна периодика и се превърна в трибуна за споделяне на научен и практически опит на български и чуждестранни специалисти чрез публикуване на авторски статии, обзори, рецензии, писма и научни информации в своите рубрики.

Редакционната колегия ще продължи да полага усилия за по-нататъшно развитие на списанието в интерес на своите читатели и неговото международно индексиране.

ЧЕСТИТ ЮБИЛЕЙ!

От Редакционния съвет

E. Titianova
Editor-in-Chief

I. Velcheva
Co-Editor

E. Christova
Co-Editor

Dear Readers,

In the past 10 years the Journal „Bulgarian Neurosonology and Cerebral Hemodynamics" established itself as a leading scientific periodical in the field of Neurology and Neurosonology in Bulgaria and caused a growing interest in the international neurologic community. It is published in both Bulgarian and English and is easily accessible online at the internet webpage of the Association.

Through informing its readers on the latest achievements in the field of Neurosonology and cerebral hemodynamics and their application in the areas of Neurology, Neonatology, Pediatrics, Vascular Surgery and other medical areas, the Journal filled up the existing gap in the Bulgarian scientific periodicals and became a tribune to share scientific and practical experiences of Bulgarian and International professionals, through the publication of original articles, reviews, book reviews, letters and scientific information within its sections.

The Editorial Board will continue to work hard for further development and growth of the Journal in the benefit of its readers and international recognition and impact.

HAPPY ANNIVERSARY!

From the Editorial Board

REGIONAL TEACHING COURSE
of the European Academy of Neurology

preceded by

9th Meeting of the Bulgarian Society of Neurosonology and Cerebral Hemodynamics

October 2-5 | 2014

Park Hotel Moskva – Sofia, Bulgaria

EUROPEAN ACADEMY OF NEUROLOGY

YEAR OF THE BRAIN 2014 EUROPE

БАНМХ BSNCH BULGARIAN SOCIETY OF NEUROSONOLOGY AND CEREBRAL HEMODYNAMICS

REGIONAL TEACHING COURSE
of the European Academy of Neurology

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9th Meeting of the Bulgarian Society of Neurosonology and Cerebral Hemodynamics

Committees

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Ekaterina Titianova (Bulgaria)

Godmother of the RTC
Vida Demarin (Croatia)

European Association of Young Neurologists and Trainees (EAYNT)
M. Moarcas

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EUROPEAN ACADEMY OF NEUROLOGY

YEAR OF THE BRAIN 2014 EUROPE

БАНМХ BSNCH BULGARIAN SOCIETY OF NEUROSONOLOGY AND CEREBRAL HEMODYNAMICS

About EAN

At the EFNS/ENS Joint Congress of European Neurology in Istanbul, June 2014 one strong unified European neurological society, **the EUROPEAN ACADEMY OF NEUROLOGY** (EAN) was founded. (www.eaneurology.org)

The ASSEMBLY OF DELEGATES is the democratic heart of EAN: 45 national delegates representing the 45 member nations of the EAN and an equal number of delegates representing the currently 900 individual members.

The EAN BOARD – 7 elected and two appointed officers:

President:	Günther Deuschl (Germany)
Vice President:	Franz Fazekas (Graz, Austria)
Secretary General:	Didier Leys (Lille, France)
Treasurer:	Marianne de Visser (Amsterdam, The Netherlands)
Member at large:	Per Soelberg Sørensen (Copenhagen, Denmark)
Chair Education Committee:	Hannah Cock (London, United Kingdom)
Chair Liaison Committee:	David Vodušek (Ljubljana, Slovenia)
Chair Programme Committee:	Paul Boon (Ghent, Belgium)
Chair Scientific Committee:	Antonio Federico (Siena, Italy)

The EUROPEAN JOURNAL OF NEUROLOGY is the official publication of the EAN.
(www.europeanjournalofneurology.com)

NEUROPENEWS is the official communication platform of the EAN.
(www.neuropenews.org)

The FIRST EAN CONGRESS will be held in Berlin, Germany on 20-23 June 2015.
(www.eaneurology.org/berlin2015)

The EAN HEAD OFFICE is located in Vienna, Austria.

AIMS OF THE EAN
Excellence in Neurology in Europe

- To increase the availability and standards of neurological services
- To advance the development of Neurology
- To encourage collaboration between European national neurological societies
- To support neurological research, encourage research collaboration
- To strengthen the standard, availability and equality of neurological education
- To raise awareness among the lay public, media, health care providers and other stakeholders, as well as law and policy makers about the burden and cost of neurological disorders and the benefits which clinical neurology can bring
- To collaborate with international, national and regional neurological associations and related international health organisation

Membership benefits are...
- free online access to the online learning platform eBrain (www.ebrainJNC.com)
- free online access to Guideline papers
- free online access to the European Journal of Neurology
- reduced fee at EAN congresses
- access to educational grants
- access to CME online

TIMETABLE

Time		FRI 3.10.2014	SAT 4.10.2014	SUN 5.10.2014	Time
08.00–08.30	Credits: 21 CME	Reception desk opening	Reception desk opening	Reception desk opening	08.00–08.30
08.30–09.00					08.30–09.00
09.00–09.30		Opening Ceremony	MODERN ASPECTS OF NEUROREHABILITATION	ADVANCE OF NEUROSONOLOGY	09.00–09.30
09.30–10.00		AGING BRAIN, STROKE AND DEMENTIA			09.30–10.00
10.00–10.30					10.00–10.30
10.30–11.00					10.30–11.00
11.00–11.30					11.00–11.30
11.30–12.00					11.30–12.00
12.00–12.30					12.00–12.30
12.30–13.00	9th Meeting of the Bulgarian Society of Neurosonology and Cerebral Hemodynamics		Lunch	Lunch	12.30–13.00
13.00–13.30					13.00–13.30
13.30–14.00		Lunch			13.30–14.00
14.00–14.30	Reception desk opening		Interactive Workshops (Hall1, Hall2, Hall3)	EXAM	14.00–14.30
14.30–15.00					14.30–15.00
15.00–15.30		Interactive Workshops (Hall1, Hall2, Hall3)		Closing Ceremony (Handout of Certificates)	15.00–15.30
15.30–16.00	General Assembly of BSNCH (for members)				15.30–16.00
16.00–16.30					16.00–16.30
16.30–17.00					16.30–17.00
17.00–17.30	Satellite Symposium of UCB "Eternity in Neurology with UCB"		City Tour		17.00–17.30
17.30–18.00					17.30–18.00
18.00–18.30	Opening				18.00–18.30
18.30–19.00	Satellite Symposium of Actavis "Secrets of Active Aging"				18.30–19.00
19.00–19.30					19.00–19.30
19.30–20.00	Dinner Ten-Year Anniversary Celebration of the Journal "Neurosonology and Cerebral Hemodynamics"	Dinner	Gala Dinner		19.30–20.00
20.00–21.00					20.00–21.00
21.00–22.00					21.00–22.00

REGIONAL TEACHING COURSE

EUROPEAN ACADEMY OF NEUROLOGY

YEAR OF THE BRAIN 2014 EUROPE

БАНМХ BSNCH BULGARIAN SOCIETY OF NEUROSONOLOGY AND CEREBRAL HEMODYNAMICS

EUROPEAN ASSOCIATION OF YOUNG NEUROLOGISTS AND TRAINEES – EAYNT
Future Perspectives for Young Neurologists in Europe

Monica Moarcas

EAYNT Secretary

Nowadays, the mobility across Europe during training has increased greatly and it represents an opportunity for young neurologists to have an insight on various medical systems, attend scientific meetings, courses in order to improve knowledge, skills and also network with colleagues.

The European Association of Young Neurologists and Trainees (EAYNT) is a non-profit organisation that was founded in 1999. Its majors aims are as follows:

- Informing young neurologists on scientific and training opportunities
- Supporting young neurologists in traveling to other countries for research or clinical training
- Representing young neurologists at international level in scientific associations
- Improving neurology training by bringing knowledge to a common level (teaching courses, online education, examinations)
- Connecting neurology trainees across the world and identifying their training needs, issues and perspectives

Becoming member of EAYNT is free and you can become member if you are Medical doctor training in neurology and related fields (neurophysiology, neurosurgery, neurosciences) or Qualified neurologist under 40 years. Registration can be done online, on our website www.eaynt.org

The EAYNT Past Office (2013) was composed of: Edina T. Varga - Past-president (Hungary), Antonella Macerollo - President (Italy), Orsolya Gyorfi - Secretary (Romania), Xenia Kobeleva - Treasurer, (Germany).

Our current Office 2014 is composed of: Antonella Macerollo - Past-president (Italy), Orsolya Györfi - President (Romania), Péter Balicza - Treasurer (Hungary), Monica Moarcăş - Secretary (Romania).

The EAYNT activities are performed in close collaboration with international organisations: EFNS, ENS, EAN, Danube Neurology Association , UEMS/European Board of Neurology, WFN, National societies of junior neurologists.

During EFNS, ENS, EAN meetings, our activities include: booth, special sessions, hospital visits, poster sessions co-chairing, abstracts reviewing, presence in scientific panels, lottery and social events for young neurologists.

Young neurologists have the oppportunity to visit hospitals in important centres during international congresses and have an insight on other medical and training systems.

During Special sessions, well known speakers offer talks on different aspects of neurology training; young neurologists have the opportunity to learn about ways to build a path in neurology – both clinical and research. At Joint Congress of European Neurology 2014, we had the honour to listen to Prof. Jose Fero, Prof. Walter Paulus and Dr. Laszlo Sztriha on „Do's and do not's in neurology". We will meet again for the Special session at the First Congress of EAN Berlin 2015.

For poster sessions at European Congresses young neurologists can be co-chair on call. This is an opportunity for young neurologists to actively interact with authors and discuss the posters, to establish connections with senior neurologists and to take responsibility early in career.

Subspecialty Scientific panels of EAN have following aims: Good clinical practice across Europe, Guidelines, Coordinating research in Europe, Improving training and continual medical education.

Chairpersons may recruit young neurologists from their own department who will be nominated official Secretary.

Lotteries at European congresses have prizes like reflex hammers, T-Shirts, but also travel grants. Social events during congresses help young neurologists network, know each other, and make new friends.

In Danube Neurology Association, EAYNT has a representative in executive Board and a meeting at annual symposia. EAYNT has a representative also in UEMS/European Board of Neurology. During World Congresses of Neurology, EAYNT has a booth thanks to WFN.

The European Board of Neurology Examination is a tool for assessment of European neurological education and improvement of its standards created by European Union of Medical Specialists (UEMS) Section of Neurology. It was first held in 2009 and is a sign of excellence, but no legal consequences attached. EAYNT offers grants for young neurologists who wish to pass the examination.

Next, I will present some of the training opportunities and grants available for young neurologists:

1. EAN Department-Department Cooperation programme 2015, 55 grants (each maximum € 1,800) for staying at a foreign department for 6 weeks

2. Fellowship programme 2015

Up to 8 grants to support research of young neurologists in departments outside their residence country.

3. EAN Spring School in Stare Splavy, Czech Republic , May 7-10th

Topics in 2015: Neurooncology, Language and higher nervous activity, Neurotraumatology.

4. Regional teaching courses

The Open Facilities for Training in European Neurology (OFTEN) Exchange programme initiated by European Board of Neurology in 2002 that aims Improvement of training on clinical skills and research by visiting acknowledged departments. There are included over 18 countries/ 106 departments and it is given full credit from national neurological and medical societies. This programme is maintained by EAYNT.

Travel grants for congresses can be EAN Congress grants and EAYNT travel grants.

Other EAN grants include:

1. EAN Investigator Award Berlin 2015 - any poster or oral presentation is eligible.

2. PK Thomas Prize Berlin 2015 - Best paper on peripheral nerve disorder.

3. EAN Tournament Uschi Tschabischer Prize for Young Neurologists.

Application when submitting abstract for First Congress of EAN Berlin 2015, 12 persons selected and receive free registration, travel grant and free accommodation.

EAYNT has always aimed to be close to young neurologists and meet their needs. There are surveys by which we tried to evaluate certain aspects of training, for example the satisfaction of trainees with their clinical training and practical skills.

In conclusion, we believe that together, we can make neurology training a better, more challenging and rewarding path to a successful career and also for the benefits of our patients.

You can find us online here:

www.eaynt.org

www.facebook.com/eaynt

Scientific Programme

THURSDAY, 2 October 2014

9th Meeting of the Bulgarian Society of Neurosonology and Cerebral Hemodynamics

(Park Hotel Moskva)

14.00 – 15.30	**Registration**
15.30 – 17.00	**General Assembly of BSNCH** *(for members)*
17.00 – 17.30	**Satellite Symposium.** *Chairpersons: E. Titianova (Bulgaria)*
17.00 – 17.20	**Eternity in Neurology with UCB.** *S. Andonova (Bulgaria)*
17.20 – 17.30	Discussion
17.30 – 18.00	**Coffee Break**
18.00 – 18.15	**Opening Ceremony**
18.15 – 19.30	**Satellite Symposium of Actavis.** *Chairpersons: E. Christova (Bulgaria)*
18.15 – 19.15	**Secrets of Active Aging.** *E. Titianova (Bulgaria)*
19.15 – 19.30	Discussion
19.30 – 22.00	**Dinner** **Ten-Year Anniversary Celebration of the Journal "Neurosonology and Cerebral Hemodynamics"**

FRIDAY, 3 October 2014

REGIONAL TEACHING COURSE of the European Academy of Neurology

(Park Hotel Moskva)

08.00 – 18.00	**Registration**
09.00 – 09.30	**Opening Ceremony** *E. Titianova (Bulgaria), V. Demarin (Croatia)*
	Greetings from the Chair of the Regional Teaching Course. *E. Titianova (Bulgaria)*
	Greetings from the Godmother of the Regional Teaching Course. *V. Demarin (Croatia)*
	Greetings from the Secretary of the European Association of Young Neurologists and Trainees. *M. Moarcas (EAYNT)*
	Greetings from Bulgarian Institutions

AGING BRAIN, STROKE AND DEMENTIA

09.30 – 10.15	**How to Face the Burden of AF with Aging to Prevent Stroke and Vascular Dementia.** *E. Azevedo (Portugal)*
10.15 – 10.20	Break
10.20 – 11.05	**Stroke and Neuroplasticity.** *V. Demarin, S. Morovic (Croatia)*

11.05 – 11.20	**Coffee Break**
11.20 – 12.05	**Present State of Thrombectomy in Acute Stroke.** *K. Niederkorn (Austria)*
12.05 – 12.10	Break
12.10 – 12.55	**Classification and Early Diagnosis of Cognitive Impairments.** *L. Traykov (Bulgaria)*
12.55 – 13.00	Break
13.00 – 13.40	**European Association of Young Neurologists and Trainees – EAYNT. Future Perspectives for Young Neurologists in Europe.** *M. Moarcas*
13.40 – 15.00	**Lunch**
15.00 – 18.00	**Interactive Workshops (Hall1, Hall2, Hall3)**
Hall 1	**Functional Transcranial Doppler in Stroke Risk.** *E. Azevedo (Portugal)*
Hall 2	**Vascular Dementia – Is There a Way to Prevent It?** *V. Demarin, S. Morovic (Croatia)*
Hall 3	**Silent Brain Infarction.** *K. Niederkorn (Austria)*
16.40 – 17.10	**Coffee Break**
18.30 – 22.00	**Dinner** *(Park Hotel Moskva)*

SATURDAY, 4 October 2014

MODERN ASPECTS OF NEUROREHABILITATION

09.00 – 09.45	**Advance in Neurorehabilitation After Stroke.** *M. Siebler (Germany)*
09.45 – 09.50	Break
09.50 – 10.35	**Brain Imaging in Neurorehabilitation.** *I. Tarkka (Finland)*
10.35 – 11.00	**Coffee Break**
11.00 – 11.45	**Combining Electrical Stimulation Mediated by Iterative Learning Control with Movement Practice using Real Objects and Simulated Tasks for Post-Stroke Upper Extremity Rehabilitation.** *A. M. Hughes, E. Hallewell, M. Kutlu, C. Freeman, K. Meadmore (UK)*
11.45 – 11.50	Break
11.50 – 12.35	**Hemiparetic Gait in Stroke Neurorehabilitation.** *E. Titianova (Bulgaria)*
12.35 – 14.00	**Lunch**
14.00 – 17.00	**Interactive Workshops (Hall1, Hall2, Hall3)**
Hall 1	**Attention Lounge – a New Concept of Neuropsychological Rehabilitation.** *M. Siebler (Germany)*
Hall 2	**Brain Imaging in Neurorehabilitation.** *I. Tarkka (Finland)*
Hall 3	**Neurological Rehabilitation using FES – Potential Underlying Mechanisms.** *A. M. Hughes (UK)*
15.40 – 16.10	**Coffee Break**
17.00 – 19.00	**City Tour**
20.00	**Gala Dinner**

SUNDAY, 5 October 2014

ADVANCE OF NEUROSONOLOGY

09.00 – 09.45	**Ultrasound Study of Intracranial Stenoses: Pre- and Post- Endovascular Treatment.** *C. Baracchini (Italy)*
09.45 – 09.50	Break
09.50 – 10.35	**Sonothrombolysis.** *M. Del Sette, L. Dinia (Italy)*
10.35 – 11.00	**Coffee Break**
11.00 – 11.45	**Ultrasound Imaging of Brain Parenchyma, Temporal Arteries and Orbita.** *M. Mijajlovic (Serbia)*
11.45 – 11.50	Break
11.50 – 12.35	**Cerebral Vasomotor Reactivity in Clinical Settings.** *I. Velcheva (Bulgaria)*
12.35 – 14.00	**Lunch**
14.00 – 15.00	**EXAM**
15.15	**Closing Ceremony** (Handout of Certificates)

EUROPEAN ACADEMY OF NEUROLOGY

YEAR OF THE BRAIN 2014 EUROPE

БАНМХ BSNCH BULGARIAN SOCIETY OF NEUROSONOLOGY AND CEREBRAL HEMODYNAMICS

REGIONAL TEACHING COURSE
of the European Academy of Neurology

LECTURERS

Prof. Elsa Irene Peixoto Azevedo Silva, MD, PhD

Education: Degree in Medicine, Faculty of Medicine of the University of Porto (1985); Postgraduate study in Intensive Care, Faculty of Medicine of the University of Porto (1997); Doctorate in Medicine, Faculty of Medicine of the University of Porto (2011).

Academic experience: Invited assistant of Neuroanatomy at the Health Sciences Superior Institute (1993-1996); Professor of Neurology and Neurosurgery in the Integrated Master in Medicine at the Faculty of Medicine of the University of Porto (FMUP) (since 2011); Coordinator of the Curricular Unit of Cerebrovascular Disease of the Doctoral Programme in Cardiovascular Sciences of the FMUP (since 2010); Current supervisor of 5 doctoral theses.

Clinical experience: Specialist in Neurology (São João Hospital, Porto since 1993); Expert in Cerebrovascular Disease, Cerebral Hemodynamics and Neurosonology with traineeship in different European centres: Toulouse, Lisbon, Angers, Heidelberg, Giessen, Barcelona; Senior neurologist (since 2009), Coordinator of the Cerebrovascular Disease Group (since 2005), of the Neurosonology Unit (since 1996), and of the Neurology support to the Emergency Department (since 1998), at São João Hospital, Porto.

Research field of interests: cerebrovascular disease, cerebral hemodynamics, neurosonology, vascular risk, vascular dementia, dizziness and syncope/syndrome of orthostatic intolerance.

Research experience: Coordinator of the cerebrovascular investigation of the Unit of Cardiovascular Investigation of FMUP (since 2007). Primary investigation areas: cerebral vascular disease, cerebral hemodynamics, neurosonology and syndrome of orthostatic intolerance / autonomic nervous system; Participated in several investigation projects with other national and international centres, on the described areas, besides coordinating some clinical trials; Organized 93 courses and meetings, some of them international; Held 289 lectures and participated in 276 in scientific presentations. She is author of 197 papers published as abstracts and 55 published as full-texts in national and international journals, 5 chapters of books and edited 4 scientific publications and has received 6 scientific awards. She collaborates with various national and international work groups, within both clinical and investigation projects.

Scientific societies: Chair of the Association of Cerebrovascular Disease of São João Hospital, one of its founders in 1997; Chair of the Portuguese Neurosonology Society (one of the founders in 2001); Vice-president of Portuguese Society of Stroke (one of the founders in 2005); Member of the executive committee of the European Society of Neurosonology and Cerebral Hemodynamics; Member of the expert panel of Neurosonology of the European Academy of Neurology; Member of work commissions of the College of Neurology of the Portuguese Medical Association, Portuguese Health Authority and collaborator/consultant in other institutions, in activities mostly related to cerebrovascular disease and cerebrovascular ultrasonography.

Prof. Claudio Baracchini, MD

Education: Secondary School Honour Graduation Diploma and Ontario Scholar, Toronto, Canada; Premedical studies (Neuroscience major) at the University of Toronto, Canada; Scholarship for academic merits, Mc Master University, Hamilton, Canada; Medical and Surgical studies at the University of Padua, Italy: 110/110 magna cum laude; Specialist in Neurology, University of Padua, Italy: 70/70 magna cum laude.

Research and clinical experience: Intern at the Institute of Physiology, University of Toronto, Canada (1983-1984); Intern, at the Playfair Neuroscience Unit, University of Toronto, Canada and Researcher at the Weston Diversified Research Centre, Toronto, Canada (1984); Intern and Resident in Neurology, University of Padua School of Medicine, Padova, Italy (1991-1999); Staff Neurologist (Clinical Neurology and Stroke Unit), Bassano del Grappa Hospital, Italy (2000-2005); Staff Neurologist (Clinical Neurology and Stroke Unit), Treviso Regional Hospital, Italy (2005-2008); Staff Neurologist (Clinical Neurology and Stroke Unit), University of Padua School of Medicine, Padova, Italy (since 2009); Director of the Stroke Unit, University of Padua School of Medicine, Padova, Italy (since 2011); Director of the Neurovascular Center (Stroke Unit + Neurosonology Lab), University of Padua School of Medicine, Padova, Italy (since 2014).

Research field of interests: Neurosonology (Cervical vessel color-coded duplex ultrasonography, Transcranial Doppler sonography, and Transcranial color-coded duplex ultrasonography); Diagnostics and therapy of cerebrovascular diseases - acute ischemic stroke, especially in the young, cervical artery dissection, acute surgical/endovascular treatment of ischemic stroke.

Publications and awards: He has authored and co-authored more than 170 publications (scientific papers and books), mainly in the fields of vascular neurology and neurosonology. Young Investigators Award at the 1st Meeting of the European Society of Neurosonology and Cerebral Hemodynamics held in Munich, Germany (1996); Investigators Award at the 5th Meeting of the Italian Neurovascular Society (1996).

Academic positions: Director of the Cerebrovascular Disease program at the University of Padua, Professor of Neurology in the Faculty of Medicine and Surgery, the Faculty of Dentistry, the Residency Program of Neurology, the School of Neurophysiopathology for Technologists; Professor of Neurology, Founder of the Neurovascular Club, University of Padova, Italy (2009); Visiting Professor in the Neurosonology Section of the Department of Neurology, Neuroangiology Unit, UniveritätsSpital, Zurich, Switzerland (2000).

Associate Editor of: BMC Neurology; Reviewer for International Journals: Stroke, Cerebrovascular Diseases, The Lancet, Neurology, Canadian Association Medical Journal, Journal of Neuroimaging.

Scientific societies: General Secretary since 2006 of the European Society of Neurosonology and Cerebral Hemodynamics (ESNCH); Member of: the International Certification Committee for Neurosonology, the Executive Committee of the Italian Stroke Association (ISA), the Executive Committee of the Italian Stroke Organization (ISO), the Executive Committee an elected future President (starting office 2015) of the Italian Society of Neurosonology and Cerebral Hemodynamics (SINSEC), the Italian Certification Committee for Neurosonology. Founder of the Italian Association for the battle against Ischemic Stroke (ALICE) and Senior Member of the Italian Society of Neurology (SIN).

Prof. Massimo Del Sette, MD

Education: High School Degree (1978); Degree in Medicine (1984); Specializations: Neurology (1988) and Legal Medicine (1991); Post-graduate training: Research Fellow Department of Neurology – University of Western Ontario – London Ontario, Canada (1991 – 1992); Research Fellow at "Robart Research Institute" – London, Ontario, Canada (1994); Master in Cerebrovascular Disease – University of Genova (2007).

Career Experience: assistant at the Department on Neurological Sciences, University of Genova, Italy (since 1989); responsible for the Neurosonology Laboratory (since 1999); Director of Neurology Unit Ospedale S. Andrea – La Spezia (since 2009).

Teaching: Neuroendocrinology at the School of Specialization in Neurology – University of Genova, Italy (1992 – 1999); Neurology at the School of Specialization in Neurology – Universitiy of Genova, Italy (since 1999);Neurology II at the School for physiotherapists – Universitiy of Genova, Italy (since 1998); coordinator of teaching course in Neurosonology at the Master in Cerebrovascular Disease – Univesrity of Genova (2006 – 2007).

Publications: co-author of more than 150 publications in national and international Journals; more than 300 lectures at local or international congresses and courses.

Membership: Chair of Neurosonology Research Group; President of the Italian Society of Neurosonology and Cerebral Hemodynamics (since 2008); Member of the Executive Committee of the European Society of Neurosonology and Cerebral Hemodynamics (since 2005); Member of the Executive Committee Associazione Lotta all'Ictus Cerebrale (since 2000); Member of the Executive Committee of the Italian Stroke Association (since 2007).

Trials: involved as "investigator" in many trials, such as IST, SAINT-I, SPARCL, ECASS III, PROFESS, DIALOGUE; Referee for STROKE, Cerebrovasc Dis, J Neuroimaging, NEUROLOGICAL SCIENCE, Calcified Tissue International.

Prof. Vida Demarin, MD, PhD, FAAN, FAHA, FESO

Professor Vida Demarin, MD, Ph.D. graduated from School of Medicine, University of Zagreb, Croatia, where she gained her Master of Science thesis and Doctor of Philosophy degree. She finished her residency in Neuropsychiatry in Sestre milosrdnice University Hospital Centre, Zagreb, Croatia.

She was Head of Department of Clinical Neurology and Centre for Neurological Sciences and Brain Research in University Hospital Centre "Sestre Milosrdnice" from May 1994. until November 2011. Under her leadership the Department became Reference Centre for Neurovascular Disorders and Reference Centre for Headaches of Ministry of Health of Republic of Croatia. From November 2011 until September 2012, she was Counselor for International Collaboration in the same institution. She was appointed Medical director of Medical Centre Aviva in September 2012.

She is a full member and fellow of Croatian Academy of Sciences and Arts. She published more than 1000 papers in national and international journals, organized and participated in numerous symposia, seminars, conferences and congresses. She mentored numerous Doctor of Philosophy and Master of Science theses, research fellows, residents and students.

Research field of interests: stroke prevention and management, neurorehabilitation, neurodegenerative disorders and dementia, headache and migraine, neuroplasticity, and neuropathic pain. She was principal investigator of numerous research projects. She is a pioneer of neurosonology in Croatia, and the founder of Summer Stroke School – Healthy Lifestyle and Prevention of Stroke that has been organized in Dubrovnik, Croatia since 1990.

For several decades she leads and organizes national stroke and cerebrovascular disease prevention programs, educating citizens, general practitioners and neurologists. All her projects are devoted to raising health awareness and improving the quality of life. She authored numerous publications dedicated to lifestyle improvement and disease prevention.

Scientific societies: Member of many Croatian and international professional societies, president of Kuratorium of International Neuropsychiatric Pula Congresses, president of Central and Eastern European Stroke Society and the Secretary General of the WFN Applied Research Group on Organization and Delivery of Care. She is member of the Executive Board of the Academy of Medical Sciences of Croatia, Fellow of American Academy of Neurology, Fellow of American Heart Association, Fellow of European Stroke Organization and member of World Stroke Organization Board of Directors, member of International Headache Society, Subspecialty Scientific Panel for Stroke, Subspecialty Scientific Panel for Headache and Subspecialty Scientific Panel on Higher Cortical Functions of European Academy of Neurology (EAN), Vice President of Croatian Brain Council, and more.

She was two terms president of Croatian Neurological Society, founder and the first president of Croatian Society for Neurovascular Disorders and Croatian Stroke Society, whose workgroup published national Recommendations for Stroke Management 2001 and 2006, as well as Evidence based Guidelines for Management of Primary Headaches 2005 and 2008, Consensus Opinion on Brain Death Diagnosing 2005, and Recommendations for the Management of Patients with Carotid Stenosis 2010. She initiated national program of stroke management, organization of stroke unit network and thrombolysis therapy in Croatia.

Dr. Ann-Marie Hughes,
MCSP, PhD

Education: BSc in Chemistry, University of Exeter (1989); PGDip in Hazardous Waste Management, University of Loughborough (1993); MSc in Information Systems, University of Southampton (1994); BSc in Physiotherapy, University of the West of England (2000) , PhD in Electronics and electrical engineering, University of Southampton (2009).

Career Experience: Technical Controller, The Boots Company (1990-1993); Financial Analyst, Financial Times (1994-1995) ; New Media Developer, Financial Times (1995 – 1996) ; Senior Neurophysiotherapist UK and New Zealand (2001 – 2005); Research Fellow, FoHs, UoS (2005 – 2011); Senior Research Fellow, FoHs, UoS (2011 – 2014); Senior Lecturer, Faculty of Heath Sciences (FoHs), University of Southampton (UoS) (since 2014)

Research field of interests: Cross-disciplinary research into the development, application and user perspectives of novel technologies (Functional Electrical Stimulation, Non-Invasive Brain Stimulation, Rehabilitation Robotics, Constraint induced Movement Therapy, and Movement Sensors) for upper limb and trunk neurorehabilitation.

Teaching: International trans-disciplinary, post-graduate education. Roles currently include: Previously responsible for Research Methods for Evidence Based Practice (HLTH6036) (over 120 MSc students) and Faculty Post Graduate Forum (over 149 PhD and DClinP students). I currently supervise 5 PhD students in addition to MSc students and deliver teaching primarily to post graduate students (DClinP and MSc).

Impact: Established global researcher and clinician network; led virtual European team on complex EU grant; organised outreach workshops; presented with Best Paper at the International Conference of Rehabilitation Robotics (ICORR) in Japan 09; ethics committee member; reviewer for: journals, (Rehabilitation Research and Development, Neurorehabilitation and Neural Repair, Presence and Physiotherapy); grants (BBSRC) and MS Society grant review panel; IEEE conferences; MRC Training Fellowship Applications; and contributed to the UK Intercollegiate Working Party for Stroke RCP Guidelines 2012. Steering Committee member for ICORR & International Industry Society for advanced rehabilitation technologies (IISART). EU Cost Action on Rehabilitation Robotics Fellow.

Ass. Prof.
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Education: Doctor of Medicine, School of Medicine, University of Belgrade (July 2001); General Practitioner License (July 2002); Master's Degree (MSc) in Neurology, School of Medicine University of Belgrade (2001 – 2007); Board certified Neurologist, Institute of Neurology, Clinical Center of Serbia, Belgrade; School of Medicine University of Belgrade (2006 – 2009).

Medical skills: Neuropsychological and behavioral examination and evaluation, Neurosonology (Extracranial/Transcranial ultrasound, Temporal arteries sonography, Orbita ultrasonography), Ultrasound examination of the brain parenchyma (basal ganglia), Stroke management (including thrombolytic therapy and sonothombolysis).

Career Experience: National expert in neuroangiology, National Society of Neuroangiology of Serbia and Medical Faculty Belgrade (since 2005); Scientific Researcher, Research Associate, Ministry of Sciences of Serbia, School of Medicine University of Belgrade (since 2009); Assistant Professor in Neurology , School of Medicine University of Belgrade (since 2012).

Main fields of interests: Cerebrovascular Disorders (genetics, path-physiology of arteriosclerosis-especially the role of insulin resistance in atherogenesis, asymptomatic carotid artery stenosis and vascular dementia, rare causes of stroke especially in young adults), Ultrasound Techniques in Neurology (Power Triplex Color Doppler, Transcranial Doppler, detection of the circulating micro emboli and cerebral vasomotor reactivity testing, sonothrombolysis), chronic headaches (co-morbidity of migraine, chronic tension type of headache, rare headaches-SUNCT, cluster headache, paroxysmal hemicranias), Neuropsychology and Dementia, Movement Disorders (neuroimaging techniques, brain parenchyma sonography).

Membership: Executive Committee of the Neurosonology Research Group of the World Federation of Neurology, Scientific Committee of the European Society of Neurosonology and Cerebral Hemodynamics, Chronic Daily Headache International Study Group of the International Headache Society-HIS, European Federation of Neurological Societies-EFNS, The Movement Disorders Society-MDS, World Stroke Organization-WSO, European Stroke Organization-ESO, Board of the National Society of Neuroangiology of Serbia, Serbian Medical Society/Chamber, President of the Scientific Committee of the Society of Young Serbian Neurologists.

Prof. Kurt Niederkorn
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Education: Medical School Graz, Austria (1973 – 1980); Residency, University Dep. of Neurology, Graz, Austria (Since 1980).

Career Experience: Faculty Member, University Dep. of Neurology, Graz (since 1988);Assistant Prof. of Neurology (1989); Asssociate Prof. of Neurology; Chief, Section of Neurosonology (1991); Professor of Neurology (1996); Vice Chairman, Dep. of Neurology Graz (1996 – 2013); Deputy Head, Section of General Neurology (2005 – at present);Head, Stroke Unit,Stroke outpatient clinic and Neurology Emergency Service Dep. of Neurology Graz (2001 – at present).

Publications: More than 220 publications; Reviewer for Stroke, Cerebrovascular Diseases, Journal of the Neurological Sciences, Journal of Neuroimaging, European Journal of Ultrasound, etc.

Memberships: European Society of Neurosonology and Hemodynamics (President 2005-2009); Neurosonology Research Group of the World Federation of Neurology (Executive Committee Member until 2009); American Academy of Neurology; American Society of Neuroimaging; Austrian Society of Neurology; Honorary member, Bulgarian Society of Neurosonology and Cerebral Hemodynamics.

Local PI: ECASS 2, 3 and 4; SPACE and SPACE2, Chrystal-AF, Endostroke, Austrian Stroke Registry, Swift-Prime.

Prof. Mario Siebler, MD

Education: Study of Medicine, University Homburg Saar (1977 – 1983), Study of Informatics University Saarbrücken (1979 – 1981), Medical Thesis in Neurophysiology (1984), Postdoctoral Fellowship in Neurophysiology (1983 – 1985), Intern in Neurology, Neurology Department of the University Homburg (1985 – 1986), Fellowship of the Deutsche Forschungsgemeinschaft for Neurophysiology Department of Neuroscience, Heinrich-Heine University Düsseldorf (1987 – 1988), Intern in Neurology at the Neurology Department of the Heinrich-Heine University Düsseldorf (1988 – 1994),Intern in Psychiatry (1992).

Career Experience: Assistant Professor in Neurology University of Düsseldorf (1994), Consultant in Neurology (1995), Organization and Leading of the Stroke Unit University Düsseldorf (1997 – 2008), Specialization in Intensive Care Medicine for Neurology and Stroke (1999 – 2008),Head of the experimental Neurophysiology Lab (1988 – 2008), Head of the Neurology and Neurorehabilitationcenter Essen/ Kettwig (since 2008).

Awards-Specialization: Claude-Bernard-Award of the University Saarland (1985), Award of excellence for cerebral hemodynamics/San Diego/ Calif. USA (1992), Edens-Award of the Heinrich-Heine-University (1993), Award of Innovation from Nordrhein-Westfalen (1994), Scientific Award for Neurochiptechnology ANIM (2007), Scientific Award for Orbitaultrasound ANIM (2008), President of the Stroke Organisation Düsseldorf (since 2002), Member of the ESNCH Board (since 2008).

Prof. Ina M. Tarkka,
PhD

Education and experience: Dr. Tarkka received her PhD at the University of Jyväskylä 1986, did many years of neuroscience research in USA and Germany and then served as Director of Research at the Brain Research and Rehabilitation Center Neuron, Kuopio. She is Adjunct Professor in Cognitive Neuroscience and Researcher in the Department of Health Sciences, University of Jyväskylä, Jyväskylä, Finland.

Research and publications: Dr. Tarkka has published over 100 scientific papers and served in a number of scientific expert positions. Her clinical experience is in human neurophysiology and neurorehabilitation. She is involved in different EU projects in scientific collaboration as well as developing European-wide Master's level education in neurorehabilitation.

Acad. Prof.
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Current positions: Acad. Prof. Ekaterina Titianova, MD, PhD, DSc is Professor of Neurology and Faculty member of the Faculty of Medicine of Sofia University "St. Kl. Ohridski". She is a Head of the Clinic of Functional Diagnostics of Nervous System at the Military Medical Academy – Sofia (since 2005) and Academician of the Bulgarian Academy of Sciences and Arts (since 2012).

Scientific activities: Acad. Titianova is author and co-author of more than 200 publications, including books. She is nominated with 5 scientific awards in the field of neurology and neurosonology.

Scientific Societies: Acad. Titianova is a President of Bulgarian Society of Neurosonology and Cerebral Hemodynamics (since 2005), Member of the Executive Committee of the WFN Neurosonology Research Group (since 2009), Editor-in-Chief of the Bulgarian Journal "Neurosonology and Cerebral Hemodynamics" (since 2005), Member of the International Advisory Boards of Journals "Archivos de Neurociencias" (Mexico) and "Neurosonology" (Japan).

Research fields: cerebrovascular disease, neurosonology, cerebral hemodynamics, hemorheology, autonomic failure, orthostatic intolerance, gait motor control, neurorehabilitation.

Prof. Latchezar Traykov,
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Career Experience: Prof. Latchezar Traykov is Head of the Neurology Department at the Medical University in Sofia, Bulgaria. He has held a series of senior positions at hospitals in his native Bulgaria, as well as in Paris, where he was Associate Professor of Neurology at the Neurological Clinic, at the Faculty of Medicine, University Paris XII.

Research field of interests: In 2001 he was qualified as University Professor at the Neuroscience Section of the National University Council of France, following scores of research activities, awards and publications. His research activities and grants have included projects on aging and dementia; Alzheimer's disease; vascular dementia; therapeutic strategies in patients with cognitive decline; and many more, spanning nearly twenty years.

Awards: Awards granted to Professor Traykov over the past sixteen years have included prizes for Best Research in Neuroscience; the Foreign Scholarship Award in Washington, USA; the France Alzheimer annual prize for best research; the Panacea Gold for special contributions to teaching, research and expert activity, as part of the Annual Prize of the Medical University of Sofia; and the Annual Prize of the Union of Scientists in Bulgaria.

Publications: Professor Traykov has authored and edited scores of articles worldwide for leading professional publications specializing in neurology, neuropsychology, geriatric psychiatry, neuroepidemiology and more.

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Membership: Member of many national and international organisations. Chair of section "Medical sciences" at the union of scientists in Bulgaria. Representative of Bulgaria at the European Neurology Board. Vice-president of the Bulgarian Society of Neurosonology and Cerebral Hemodynamics.

How to Face the Burden of AF with Aging to Prevent Stroke and Vascular Dementia

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Key words:
acute stroke, anticoagulation, atrial fibrillation, stroke prevention, vascular cognitive impairment

Atrial fibrillation (AF) is undoubtedly one of the major hazards of contemporary medicine. Its prevalence is increasing, especially in the elderly, and AF-related cardioembolism is becoming the most frequent cause of stroke in this age group. This scenario is aggravated by the fact that cardioembolic stroke is frequently associated with a high morbimortality. AF also contributes to the vascular cognitive impairment, either through symptomatic acute ischemic cerebral infarcts, and/or through the multiple small, only apparently silent, cardioembolic ischemic lesions.

It is well settled that with appropriated treatment AF cardioembolic risk decreases significantly. Anticoagulation therapy is particularly effective in reducing the cardioembolic risk after a stroke and when administered to aged people. However, the ideal is to use it for preventing a first stroke, in primary prevention.

In order to deal with the burden of this enormous disease, each country warrants a multidisciplinary approach, involving correct identification of AF, even if paroxysmal, individual patient risk assessment, and an adequate stroke preventive treatment.

Fortunately, there have been important scientific breakthroughs on diagnosis and treatment of AF. Paroxysmal AF presents the same cardioembolic risk as the continuous AF, although it is often difficult to diagnose. Particularly in the case of a cryptogenic stroke with embolic characteristics, paroxysmal AF has to be exhaustively searched and might require long-term cardiac rhythm monitoring systems, which have been recently developed. Other new achievements are the therapeutic advances in oral anticoagulation treatment, allowing increased efficacy and safety, along with a better convenience to the patient.

All these new approaches are changing the paradigm of the acute stroke management, challenging the stroke unit neurologist.

Burden of atrial fibrillation in public health and its consequences

What is atrial fibrillation?

Atrial fibrillation (AF) is the most common type of cardiac arrhythmia. It consists in rapid, disorganized electrical signals that cause the atria to fibrillate, resulting in irregular contractions not strong enough to pump the blood completely into the ventricles. The subsequent atrial blood stasis leads to thrombus formations that can be pumped into the systemic circulation, possibly causing arterial thromboembolism, with ischemic stroke being the most feared clinical embolic event [9].

Atrial fibrillation prevalence

AF prevalence is continuously increasing, mainly amongst the elderly. The prevalence of AF in the general population is approximately 1%, increasing from 0.1% in younger adults (<55 years) to 9% in those aged 80 years or more [10].About 70% of patients with AF are between 65 and 85 years old and the prevalence increases 10% per decade of life after the age of 50 [7].

It should be noted that a larger proportion of the world population is now more elderly than ever before, and recent estimates suggest that by 2025 there will be 1.2 billion individuals worldwide with age ≥60 years. Consequently, the projected number of people with AF is anticipated to increase. The increased risk of AF associated with male gender and ageing were clearly showed by the ATRIA and Rotterdam studies [15].

Atrial fibrillation and vascular risk

AF can result in multiple serious consequences, such as stroke, heart failure and death. Regarding its association with strokes, AF is an independent risk factor, increasing the risk in about fivefold [31]. In fact, one in six strokes occurs in patients with AF[8].

The ischemic stroke rate among patients with AF averages 5% yearly, [9] but varies greatly depending on individual clinical characteristics such as age, sex, race/ethnicity, and associated stroke risk factors. History of stroke or transient ischemic attack (TIA) identifies those patients with a high stroke risk averaging 10% yearly [29]. Also, studies have shown that patients with AF who experience a stroke are more likely to have a second stroke than those without AF [21].

There is also evidence that strokes in patients with AF are more severe and the outcome is markedly worse compared with strokes in patients with normal sinus rhythm, as was shown in the Copenhagen Stroke Study [18].

AF is also an independent risk factor for mortality, conferring a twofold increased risk of death, and is an independent risk factor for heart failure, which can further aggravate AF, worsening overall patient prognosis [30].

Vascular cognitive impairment and atrial fibrillation

The vascular cognitive impairment (VCI) concept intends to emphasize the need to prevent the development of dementia. The high prevalence of VCI and the necessity of prevention strategies targeting vascular risk factors highlight its importance in AF. AF conveys a strong risk of cumulative brain injury and cognitive morbidity, which can be prevented with pharmacological treatment [5].

Several studies demonstrated that AF can lead to cognitive impairment and eventually to dementia [22].

Efficacy of anticoagulant treatment

With appropriated treatment, atrial fibrillation cardioembolic risk decreases significantly.

Hart and colleagues performed a meta-analysis of clinical trials (n=6), showing that warfarin reduced the relative risk of stroke in 64% compared with the placebo, and that reduction in stroke risk is greater for secondary prevention [13].

Even when compared with dual antiplatelet therapy, reduction of stroke risk is significantly higher with vitamin K antagonists, as warfarin [17].

Nevertheless, vitamin K antagonists have several drawbacks, including:

- unpredictable pharmacology leading to a variable inter-patient dose,
- a variable intra-patient dose due to multiple food and drug interactions,
- a narrow therapeutic window, which, coupled with unpredictable pharmacology, necessitates regular coagulation monitoring and dose adjustments,
- an increased risk of stroke or bleeding coinciding with failure to stay within the therapeutic range,
- consequent reluctance to prescribe in practice due to fear of bleeding or intracranial haemorrhage, particularly in elderly patients.

Fortunately, several new oral anticoagulants have been developed in the last years, being approved for preventing cardioembolic risk in patients with non-valvular AF, namely dabigatran, [4] rivaroxaban [25] and apixaban [11]. These drugs have numerous advantages over the older warfarin, including:

- a more selective mode of action (i.e. targeting a single coagulation factor), resulting in predictable pharmacokinetics and pharmacodynamics and few interactions with drugs and food;
- the possibility of being administered at fixed doses without routine coagulation monitoring;
- offering an improved benefit/risk profile in patients with AF [16].

The main disadvantages of these new oral anticoagulants are the lack of sufficiently accurate tests to evaluate the coagulation status of the patients and the difficulty in rapidly reversing the anticoagulant effect of these drugs.

How to face the atrial fibrillation burden:

Detection of AF

It is crucial to detect AF before and after a cardioembolic stroke. The clinician should take all the opportunities to check the patient's cardiac rhythm, as in the physical examination at each visit. If there is a suspicion of arrhythmia by the doctor, or if the patient has this complaint, an electrocardiogram should be performed. However, if a paroxysmal AF is suspected, it should be searched with a 24-hour electrocardiogram monitoring, a 7- or 30-day external event recorder, or even an implantable cardiac monitor [2, 19].

In the acute stroke scenario, the generalized recommendation for at least 24 hours of hemodynamic monitoring in a stroke unit might not be enough for diagnosing paroxysmal AF, since it was shown in a study that its median detection time was 43 hours, emphasizing the importance of longer continuous monitoring [12].

In the acute stroke the neurosonological study of the cervical and cerebral arteries may suggest a cardiac aetiology, which can be important in the case of a paroxysmal AF. In fact, the absence of significant arterial extra- and intracranial pathology (such as atherosclerotic plaques, arterial dissection or other) in the case of a patient with a non-lacunar stroke is highly suggestive of an upstream (cardiac) source of an embolus. Moreover, initial occlusion of a vessel at a bifurcation followed by spontaneous recanalization (the timing of recanalization may vary widely with the correspondent clinical consequences) or documentation of active embolization through the detection of microembolic signals (MES) by transcranial Doppler are also indicative. Lastly, even if the exam is not performed on the first day, Doppler hemodynamic signs of post-ischemia hyperaemia in a symptomatic territory suggest a recent revascularization of an embolic occlusion [1].

The problem of cryptogenic strokes, which are

related to a persuasive evidence of frequently being thromboembolic (Embolic strokes of Undetermined Source – ESUS), have recently to planning randomised trials to test direct-acting oral anticoagulants for secondary prevention of these ESUS [14].

Preventing cardioembolic strokes

Individual risk assessment. Cardioembolic risk is not uniform in all patients with AF. The Stroke Risk in Atrial Fibrillation Working Group performed a systematic review of studies using multivariate regression techniques to identify independent risk factors for stroke in patients with AF, and reported absolute stroke rates in subgroups of patients with these risk factors collected [29]. This lead to the CHADS2 and later to the CHA2DS-2VASc risk score, considering as risk factors congestive heart failure, hypertension, age (2 points if >75 years, 1 point if 65-74 years), diabetes, prior stroke/TIA (2 points), vascular disease and female gender [24]. For treatment purposes, anticoagulation is recommended with a score of at least 2 [6].

On the other hand, a score for haemorrhagic risk was also proposed. The HAS-BLED scores for hypertension, abnormal renal/liver function, stroke, bleeding condition, labile INR, being elderly and drugs/alcohol. Some of these risk factors for bleeding are also risk factors for stroke related to AF which complicates evaluation of benefit/risk.

The predictive accuracy of HAS-BLED in the AF cohort of patients from the Euro Heart Survey was good [26]. The 2010 ESC Guidelines state that it would seem reasonable to use the HAS-BLED score to assess bleeding risk in patients with AF on the basis that a score of ≥3 indicates 'high risk'. In addition, some caution and regular review of the patient would be needed following the initiation of antithrombotic therapy [6].

Starting anticoagulant therapy. For patients with a CHA2DS2-VASc score of ≥ 2 it is recommended an oral anticoagulation therapy using an adjusted dosing of vitamin K antagonists (VKA) (preferably within the international normalized ratio [INR] of 2.0-3.0), one of the new oral anticoagulation drugs (direct thrombin inhibitors – dabigatran – and direct Factor Xa inhibitors – rivaroxaban, apixaban) [2]. These new oral anticoagulation drugs (NOAC) offer better effectiveness, reliability and convenience in comparison with the VKA (warfarin, acenocoumarol); thus, if oral anticoagulation therapy is recommended, these should be considered [2]. When electing a particular NOAC, it is important to take into account, amongst other issues, the concomitant drugs that the patient is taking, as there can be contraindications or potential interactions between them, the NOAC and the renal function.

Before starting the anticoagulation therapy, the following should be considered:

– As in the case of beginning a therapy with VKA or other NOAC or with platelet antiplatelet drugs, the reversible risk factors of haemorrhage should be under control (blood pressure, concomitant drug therapies – aspirin and non-steroidal anti-inflammatory drugs, alcoholic ingestion) [2];

– Every patient who starts therapy with any of the NOAC should undergo an initial evaluation regarding hemoglobin, platelets, coagulation, renal function and hepatic function [16], and should be alerted to the necessity of subsequent regular evaluations.

– The patient should be aware of the importance of a strict adherence to the therapy, understanding that its withdrawal leads to an immediate decline of the prevention [3].

Challenges in acute stroke management with the NOAC

Ischemic stroke

Acute stage. Oral anticoagulation represents a frequent challenge for the emergency management of ischemic stroke (IS), since a considerable proportion of IS patients under anticoagulation therapy appear to be eligible for thrombolysis [27].

According to current recommendations, the intravenous thrombolytic therapy with rtPA can be performed until 4.5 hours after the beginning of ischemic stroke symptoms, and is contraindicated in patients under anticoagulation therapy [16].

Since the half-life of NOAC is about 8-17 hours, according to some authors, the thrombolytic therapy cannot be performed in the first 48 hours after the taking of a NOAC (corresponding to 4 half-lives) [16]. However, as noted by the European Heart Rhythm Association (EHRA), this recommendation is arbitrary and has never been tested [16]. Therefore, one of the most important issues in the scenario of a patient with ischemic stroke taking a NOAC is to confirm the time of the last anticoagulation drug taking, along with analysing the renal function and proceeding to the coagulation study, despite the fact of this being less accurate with these NOAC.

It is possible to consider endovascular recanalization by thrombectomy in the acute stroke anticoagulated patient.

During the ischemic stroke's acute stage the anticoagulation therapy should be discontinued [16]. It should be investigated whether the stroke was a result of lack of adherence to the therapy. If the stroke has happened despite a strict adherence

to the therapy, other potential aetiologies should be excluded, besides the eventual cardioembolism.

Post-acute phase. Regarding the post-acute phase, there are no clinical studies that suggest an optimal time to restart the anticoagulation therapy, which might vary between 1 to 3 weeks, depending on each case in particular. This decision may take into account the patient's thrombotic risk, the ischemic lesion dimension and the presence of haemorrhagic transformation. In order to evaluate these conditions and help the clinic in making a decision before starting the anticoagulation therapy, a CT scan is recommended.

Haemorrhagic stroke

Acute stage. There are no specific data regarding actions to take in the case of cerebral haemorrhages in patients treated with any NOAC. Potentially, the action could be similar to that used for patients treated with VKA – to stop immediately the oral anticoagulation therapy, implement support therapy, and consider using prothrombin complex [16].

Post-acute stage. There are no available/known data related to the restart of oral anticoagulant therapy after a haemorrhagic stroke. It can be restarted 10 to 14 days after the haemorrhagic stroke when the cardioembolic risk is high and the risk of suffering another haemorrhagic stroke is low [16]. Nonetheless, a retrospective study that estimated the risk in a specific cohort suggested that the anticoagulation restart could be delayed to 10 to 30 weeks after the haemorrhagic stroke [20]. It should be reminded that the occurrence of spontaneous intracerebral haemorrhage under VKA or NOAC therapy makes these oral anticoagulation drugs contraindicated, unless when the cause of the haemorrhage is controllable [25]. Regarding aetiology, it should be noted that the hypertensive small vessels condition might be easier to control, through an effective treatment of the arterial hypertension, while cortical haemorrhages associated with amyloid angiopathy tend to recur more easily [23] and are not susceptible of prevention, thus contraindicating the restart of anticoagulation therapy [28]. Non-pharmaceutical prevention strategies (e.g.: ablation or occlusion of the auricular appendix) might be considered as an alternative to the oral anticoagulation drugs, when its restart is contraindicated [31].

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Stroke and Neuroplasticity

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Key words:
functional neuroplasticity, neuroplasticity, neurorehabilitation, stroke, structural neuroplasticity

Stroke is one of the leading causes of mortality and disability in modern countries. Clinical manifestation of stroke is rapidly developing loss of brain function due to disturbance in the blood supply to the brain. Challenging the brain with different tasks creates new neural connections and intensive exercise leads to improvement in neuroplasticity.

Neuroplasticity can be defined as brain's ability to change, remodel and reorganize for purpose of better ability to adapt to new situations. The concept of neuroplasticity is quite new, and it is one of the most important discoveries in neuroscience. The fact is that neural networks are not fixed, but occurring and disappearing dynamically throughout our whole life, depending on experiences. While we repeatedly practice one activity such as a sequence of movements or a mathematical problem, neuronal circuits are being formed, leading to better ability to perform the practiced task with less waste of energy. Once we stop practicing a certain activity, the brain will redirect these neuronal circuits by a much known 'use it or lose it' principle. Neuroplasticity leads to many different occurrences, such as habituation, sensitization to a certain position, medication tolerance, even recovery following brain injury.

Stroke is a major health problem despite the great efforts made worldwide to fight against it. Despite therapeutic achievements to treat ischemic stroke patients, prevention remains the most powerful strategy to cure this heterogeneous and multifactorial disease caused by the combination of vascular risk factors, environment, and genetic factors. It remains one of the leading causes of mortality and disability in modern countries.

The brain damage caused by a stroke may result in the loss of cerebral function. However, the brain can use neuroplasticity to adjust itself functionally, by reorganizing the cortical maps, which contributes to the stroke recovery. The changes in the cortex organization include an increase in the number and density of dendrites, synapses and neurotrophic factors synthesis which results in two ways: unmasking of existing neuronal circuits and establishing of new neuronal circuits. Term neuroplasticity comes from Greek word "plastos" which means pliable; it means that neurochemical, synaptic, receptor and functional reorganization in brain results in new functional possibilities. After damage of the motor cortex, changes of activation in other motor areas are observed. These changes occur in homologue areas of the non-affected hemisphere which can substitute for the lost functions or in the intact cortex adjacent to the damage. Due to these cortical reorganizations, which begin from one to two days after the stroke, and can be extended for months, the patients can recover, at least in part, their lost abilities. The recovery of functions of the limbs which is promoted by plasticity is more difficult to occur, due to a phenomenon known as "learned non use". With the loss of a brain area's function, the body part that was linked to this area is also affected and its mobility power is lost too. As the patient can not move his most affected limb, he compensates this using the other limb. Thus, after a certain period, when the damage effects aren't present anymore and brain adaptations happen, the movements could be recovered, but the patient has already 'learned" that the limb is no longer functional [1]. Cognitive abilities like processing speed, memory and reasoning start to decline in our late twenties. Normal aging process and many different neurological disorders like stroke, dementia, Alzheimer's and Parkinson's disease, Huntington disease, multiple sclerosis and acquired brain trauma contribute to the decline of our cognitive abilities.

About 120 years ago, William James was the first to suggest the theory of neuroplasticity in his work Principles of Psychology [2]. He suggested that human brain is capable for continuous functional changes. Polish neuroscientist Jerzy Konorski was the first to define the term 'neuroplasticity' in 1948. Konorski suggested a theory by which neurons which have been activated by closeness of an active neural circuit, change and incorporate themselves into that circuit [3]. Donald Hebb, a Canadian psychologist established a Hebb's rule, defined also as pre-post coincidence, implying that changes of biochemical processes in one neuron can stimulate neighboring simultaneously activated synapses, this being the basic principle of synaptic plasticity [4]. Paul Bach-y-Rita is the pioneer in demonstrating neuroplasticity on actual cases, claiming

that healthy regions of the brain can take over the functions of injured parts of the brain. This was the basis of his treatment for people who suffered vestibular damage. He patented an appliance which when connected to one's tongue, stimulates receptors by vibrations in a frequency and amplitude in correlation with pixel analysis from the surroundings [5, 6, 7]. Edward Taub supported research and developed first real and applicable treatments for patients. He proved, first using rhesus monkeys, then on humans, that tying up of healthy half of the body in case of hemiplegia, "forces" the damaged part of the brain to faster rehabilitation [8, 9, 10]. Michael Merzenich is yet another neuroscientist who left his mark in the field of neuroplasticity. He designed software for in order to help people with learning difficulties [11, 12].

All these scientists had to fight against an academic dogma which disapproved the existence of adult brain neuroplasticity, except during developmental phase. Until the Decade of the brain (1990-2000), the word 'neuroplasticity' itself, lead to articles not being published in prestigious journals. When asked, Eric Kandel, a Nobel Prize winner in medicine, said that neuroplasticitiy is what marked the Decade of the brain.

Neuroplasticity is a general term, defining the fact that the brain changes, recognizing the need for further definition of the term. We distinguish structural from functional neuroplasticity.

Structural neuroplasticity: synaptic plasticity refers to changes in the strength between neurons (synapses), chemical or electric meeting points between brain cells. Synaptic plasticity is a general term, and the name itself has no meaning other that something changed within the synapse, but can include many specific processes such as long-term changes in the number of receptors for certain neurotransmitters, or changes where some proteins are being synthetized more within the cell.

Synaptogenesis refers to formation and fitting of synapse or group of synapses into a neural circuit [13]. Structural plasticity is a normal marking of fetal neurons during brain development and is called developmental plasticity, including neurogenesis and neuronal migration. Neuronal migration is a process in which neurons travel from their 'place of birth' in fetal ventricular or subventricular zone, towards their final position in the cortex.

During development, brain areas become specialized for certain tasks such as processing signals form the surrounding areas through sensory receptors. For example, in occipital brain area, the fourth layer of cortex hypertrophies in order to receive signals from the visual pathway [14].

Neurogenesis is formation of new neurons. It is a process which mainly takes place during brain development, even though in the last decade neurogenesis was found in adult brain as well. On the other hand, neuronal death occurs throughout life, due to brain damage or programmed cell death. Other forms of structural neuroplasticity include changes in white or gray matter density which can be visualized by magnetic resonance.

Functional neuroplasticity: functional neuroplasticity depends upon two basic processes, learning and memory. They also represent a special type of neural and synaptic plasticity, based on certain types of synaptic plasticity causing permanent changes in synaptic effectiveness [15]. During learning and memory permanent changes occur in synaptic relationships between neurons due to structural adjustments or intracellular biochemical processes.

When looking at neuroplasticity on molecular level, all types of synaptic plasticity share neurotransmitter exocytosis modulation, on the level of one single synapse or among a larger neuronal network. Synaptic plasticity mainly depends on receptors binding neurotransmitters. Mental events activate a large neural molecular cascade, including regulatory factors referring to DNA and RNA [16]. Research on long term changes within the synapse consider different types of memory based on different mechanisms. Within the cortex, glutamate receptors play the key role, as glutamate is the most important excitatory neurotransmitter. If several impulses, from neighboring neurons, in a very short time, activation of metabotropic glutamate receptors (NMDA) occurs. This enables calcium influx which participates in protein synthesis, and permanently changes postsynaptic neuron [17].

After establishing the fact that brain has a possibility of remodeling its own neural maps, the main question for neurorehabilation medicine is how to direct this neuroplasticity to regain lost functions caused by a neurologic deficit. This emphasizes the need to neuroanatomically define every neurologic lesion. When we know which neural pathway is damaged, we can start looking for bypasses.

Movement rehabilitation: when we learn complex movements, the brain firstly recognizes basic motoric movements, and divides them and stores them into a given model which is then remembered. The same network of neurons will activate every time we observe, think, or make a certain movement, or hear sounds which remind us of that movement. If we focus on repetitive movements, it is important to understand the purpose of the movement. For example, for a patient practicing hand pronation, the movement itself is not the purpose; the purpose is for him to be able to open the door again. This way we can stimulate other neuronal circuits which can lead to execution of this

final goal. Neurological rehabilitation must focus on expediency of the movement. This makes familiarizing with patient's habits before stroke very important. Most complex movements that we perform, we were first observing during childhood. It is helpful to repeat these movements during rehabilitation process. Ventral premotor cortex and base of parietal lobe are cortical areas belonging to mirror neuron system [18]. These areas have shown to be great neuroanatomical target areas for rehabilitation exercises. The goal is to reach their activation through any connected healthy part of the cortical network. The mirror neuron system will activate differently in every person, depending on individual's level of practice of specific movement. For example, if a patient played a guitar and danced tango prior to stroke, the observation of these activities itself will strongly activate his mirror neurons, which leads to stimulation of larger network area and reconnection of large number of synapses.

Neuronal processing of different signals: in 1821, a French soldier named Charles Barbier, visited a Royal institution "night writing", in Paris, presenting his invention, a code of 12 dots which offer possibilities to soldiers to communicate and share information on the battle field, without the need for speech. Usage of the code showed to be too difficult for soldiers, but not for a blind boy from that institution, Louis Braille. Braille lowered the number of dots from 12 to 6, and published the first Braille book in 1829. In 1839 he added mathematical and music symbols [19]. How can a blind person process and translate position of the dots so fast? If the experience is changing dramatically or parts of the brain are damaged, parts of the brain can change their function without structural changes. From this example, visual cortex in a blind person, if it's not receiving information from the visual pathway, it can process the sense of touch. 150 years later, Uhl and his coworkers proved that tactile reading in blind subject activates the occipital, visual part of the cortex [20]. Remodeling of brain maps after brain damage is a revolutionary term which opened a pathway for new understanding of neurorehabilitation [21]. After accepting the fact, the future of neurorehabilitation lies in defining neural pathways and ways we can regain lost function by using bypass pathways in the brain [22].

Our brain is constantly changing during lifetime. During fetal development structural changes are dominant, such as neurogenesis and migration of neurons, while in adult brain the dominant type of neuroplasticity is functional, allowing the brain to constantly adapt to environment and injury. The greatest challenge for neurorehabilitation in the future is finding and defining major and minor neural pathways, and then aim to support neuroplasticity of compensatory neural circuits.

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Classification and Early Diagnosis of Cognitive Impairments

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Key words:
Alzheimer's disease, cognition, early diagnosis, mild cognitive impairment, vascular dementia

The recent developments in drug treatments for Alzheimer's disease (AD) and other dementias, have highlighted the importance of early diagnosis and the need to characterize the cognitive profile of the earliest stages of the disease. The final result in dementia is well known to the physicians and it is not difficult to make the diagnosis especially in its late phases. However, several problems remain in terms of diagnosis, particularly in its early stages. To provide a few examples that will be developed in this chapter, the clinical diagnosis of very early dementia and its differentiation from normal aging remains problematic. Recent research has identified a transitional state between the cognitive changes of normal aging and AD, known as Mild Cognitive Impairment (MCI). Another problem is the differential diagnosis between different forms of dementia which is complicated by the fact there is a genuine overlap between the pathology of AD and the pathology observed in many other disorders.

This presentation will discuss briefly the neuropsychology of normal aging and of the entity known as benign senescent forgetfulness or age-associated memory impairment. It will then review the rationale of the criteria that have been proposed to diagnose patients with MCI. An important issue in the early diagnosis of AD is also the differential diagnosis with VaD. Especially the new concept of Subcortical Vascular Cognitive Impairment (VCI) will be discussed. In this context, a better understanding of neuropsychological differences between MCI and VCI may have important implications for the differential diagnosis of these disorders.

The recent developments in drug treatments for AD have highlighted the importance of early diagnosis and the need to characterize the cognitive profile of the earliest stages of the disease. Recent research has identified a transitional state between the cognitive changes of normal aging and AD, known as MCI [2, 14].

The diagnosis of AD is often difficult, especially in its early phases and this is due to several reasons9. First of all, the onset of AD is always insidious and the disease tends to occur in elderly persons with frequent changes in cerebral functions due to some other pathology or to "normal" aging. In addition, the clinical signs of AD tend to be non-specific, especially in the early stages of the disease, and they tend to vary considerably from case to case. The neuropathological lesions, albeit more specific, are not readily accessible to routine imaging techniques. Finally, to complicate matters even further, there is a genuine overlap between the pathology of AD and the pathology observed in many other disorders.

This presentation will discuss briefly the neuropsychology of normal aging and of the entity known as benign senescent forgetfulness or age-associated memory impairment. It will then review the rationale of the criteria that have been proposed to diagnose patients with MCI. An important issue in the early diagnosis of AD is also the differential diagnosis with Vascular dementia (VaD). Especially the new concept of Subcortical VCI will be discussed. Since subcortical VaD sometimes presents gradual progression, extrapyramidal signs, depression and leukoaraiosis or white matter abnormality on CT or MRI which are also frequently observed in AD, it is probably the most difficult to discriminate clinically from AD. In this context, a better understanding of neuropsychological differences between MCI and VCI may have important implications for the differential diagnosis of these disorders.

Dementia and normal aging

Our understanding of neuropsychological changes in normal aging has evolved considerably in recent past [6, 10] . Most studies agree that age is accompanied by an overall decline in cognitive functions as measured by IQ tests. A more detailed analysis shows that, in general, verbal functions (corresponding to so-called crystallized intelligence are relatively preserved in aging subjects, while non-verbal functions ("fluid intelligence") tend to show a decline. This is reflected by the results of classical intelligence tests

such as the Wechsler Adult Intelligence Scale (WAIS): up to age 75, there tends to be little or no changes at verbal subtests such as vocabulary or arithmetic. In contrast, digit-symbol substitution, object assembly and other performance subtests often show changes starting at age 60 [16]. More detailed neuropsychological tests show that in general, the most important cognitive changes involve attention (particularly divided attention), some visuospatial functions and some processes involved in learning and remembering. Some authors have found, however, that if assessment is restricted to elderly subjects who are completely free of any disease, the effect of aging on cognitive functions is mild. A working party of the International Psychogeriatric Association (IPA) in collaboration with the World Health Organization (WHO) proposed diagnostic criteria for "Aging-Associated Cognitive Decline" (AACD) to categorize subjects with cognitive decline falling short of dementia [16]. The criteria include the presence for at least 6 months of subjective gradual cognitive and objective evidence of abnormal performance in any principal domain of cognition. The abnormality is defined as performance at least one standard deviation below the age and education norms in well standardized neuropsychological tests. Thus, the diagnosis of AACD identifies persons with subjective and objective evidence of cognitive decline which does not evolve toward a dementia [17]. A concept akin to AACD is included in DSM-IV as a "age-related cognitive decline" (ARCD) and defined as "an objectively identified decline in cognitive functioning consequent to the aging process that is within normal limits given the person's age".

In conclusion, it is important to stress that a major loss of episodic memory and a sizable intellectual decline are not part of normal aging and represent clear indications for further workup.

The challenge of early detection Alzheimer's disease or amnestic Mild Cognitive Impairment

Patients with MCI have a memory impairment that is higher than that expected for their age, yet they do not meet commonly accepted criteria for dementia or AD because their cognitive deficits are limited to memory alone and their everyday abilities are preserved [7]. Although MCI can present a variety of symptoms, when memory loss is the predominant symptom it is termed "amnestic MCI" and the risk is higher for the development of AD [1]. These patients progress to AD at a rate of 10% to 15% per year, as compared to elderly individuals without MCI, who convert at rates of 1% to 2%. However, subsequent work has also indicated that MCI is heterogeneous in its clinical presentation and should be considered in a broad clinical context [23]. The principal cognitive impairment can be amnestic, single nonmemory domain or involving multiple cognitive domains (with or without a memory impairment).

Several studies have suggested that an impairment of memory is most common in amnestic MCI and is the fundamental aspect of cognition to evaluate. Collie [7] et al reported verbal episodic memory performance in an MCI group that was as impaired as that seen in mild AD. However, the same MCI group's performance on measures assessing other cognitive domains (naming, executive functions, etc.) was equivalent to that of healthy older controls. Other studies of MCI report cognitive deficits similar to those described by Petersen and colleagues. Grundman [13] in line with the concept of amnestic MCI, we would like to stress on the benefits of the Buschke's FCSR test [12] usage, in spite of the studies that examined memory functioning in MCI using free recall measures [1, 2]. Our recent findings [22] show that MCI patients recalled significantly fewer words on immediate and delayed free recall than did matched control participants and show, in addition, lesser efficacy of cued recall. Similar results were obtained by Grober et al. [12] who investigated learning and retention in participants who later developed AD. Considered together, our findings with those of Grober et al. [12] indicate that detection of MCI and very early AD may be best accomplished by using robust learning tests that control cognitive processing.

However, in recent years, the literature has reported that, while episodic memory is the hallmark of patients with amnestic MCI, they are impaired on a variety of tasks that have commonly been considered a measure of executive functions [5]. Executive functions are encompassing a number of cognitive abilities which generally have been conceptualized as controlling or guiding behavior in a top-down fashion such as decision-making, planning, self monitoring, and behavior initiation, organization and inhibition [4].

Some authors suggest that executive deficits appear early in AD but the initial stage of the disease, known as MCI is characterised by amnesia alone with profound loss of episodic memory, despite intact executive functions [10]. Longitudinal studies employing neuropsychological assessment in small groups of subjects have suggested that, following the amnesia-only phase, deficits in executive functions and/or semantic memory arise before all domains of cognitive processing become affected [18]. Other studies have shown both episodic memory and executive function tasks to be predictive of latter onset of AD, [22]

and some, indeed report executive functions to be equally predictive for the latter development of AD. Thus, although an episodic memory deficit is generally considered to be the first sign of AD, these longitudinal results support a multiple pattern of deterioration prior to AD. Similarly, recent studies show, that when the clinical syndrome of MCI evolves on a neurodegenerative basis, the multiple-domain type of MCI has a less favorable prognosis than the amnestic type and may represent a more advanced prodromal stage of dementia [3].

The challenge of early detection of Vascular Dementia or the concept of Subcortical Vascular Cognitive Impairment

VaD is known as the second most common form of dementia. In recent years, practical as well as theoretical considerations have engendered a strong interest in recognizing the very early VaD [6, 21]. The cognitive impairment related to cerebrovascular disease (CVD) may be more preventable and patients with CVD could benefit from therapy. This possibility underlines the importance of early detection and accurate diagnosis of VaD.

Although relatively easy to define, VaD has proved difficult to diagnose because of the wide variability in mechanisms, brain changes, syndromes, and course. At present, the current criteria for VaD such as the DSM-IV, select an heterogeneous group and may have biased findings in research studies and clinical trials. In 1993, the NINDS-AIREN International Work Group [20] proposed diagnostic criteria for VaD focusing on the delineation of the clinical subtypes of VaD, consistent with the heterogeneity of dementia syndrome from CVD. Accordingly, the main subcategories of ischaemic VaD include multi-infarct dementia, strategic single-infarct dementia, and small-vessel disease with dementia.

Many studies dedicated to development of drug treatment for VaD suggested that subcortical VaD, caused by small vessel disease, represents a more homogeneous subtype for clinical trials [11]. However, there are some limitations in the current criteria for the diagnosis of subcortical VaD, such as the definition of the cognitive syndrome and the necessity of relationship between onset of dementia and CVD.

To further refine the criteria for subcortical VaD, Erkintunti et al. [11] have proposed a modification of the NINDS-AIREN criteria as a new research criteria for subcortical VaD. This proposition provides a sharper delineation of the clinical and the brain imaging features of patients with subcortical VaD. For example, according to these criteria, the cognitive syndrome in subcortical VaD includes both a dysexecutive syndrome and memory impairment caracterised by predominantly retrieval deficit, however there is a need to identify cognitive test-batteries for screening, diagnosis and follow up.

An important issue in the early diagnosis of VaD is also the differential diagnosis with AD. Since subcortical VaD sometimes presents gradual progression, extrapyramidal signs, depression and leukoaraiosis or white matter abnormality on CT or MRI which are also frequently observed in AD, it is probably the most difficult to discriminate clinically from AD. In this context, a better understanding of neuropsychological differences between VaD and AD may have important implications for the differential diagnosis of these disorders.

Recently, we found that VaD patients showed fewer impairment on episodic memory measures than AD patients. The results show a noticeable impairment on free recall, some deficit on cued recall, and quasi-normal recognition memory in VaD patients relative to controls. This deficit should be considered a retrieval defect of memory, patients being helped by semantic cues. In contrast, AD patients show lesser efficacy of cued recall (as assessed by the proportion of maximum possible recall obtained by total recall) and impaired recognition as compared with VaD. Our findings indicate that use of a cued recall and recognition procedures significantly enhance the ability to discriminate between VaD and AD. In addition, patients with VaD have a significantly greater number of perseverative errors during tasks that assess "frontal" lobe functions, while AD patients exhibit more perseverations on tests of semantic knowledge.

It might be reasonable to interpret the findings in terms of topographical distribution of neuropathology in AD and subcortical VaD. While AD is characterised by medial temporal lesions early in the course of the disease, the subcortical VaD seems to involve predominantly basal ganglia and frontal white matter lesions[30]. It is generally agreed that memory is supported by multiple neural systems, with particular involvement of the medial temporal structures Haxby [15]. However, episodic memory disturbance reflecting more pronounced impairment on free recall than recognition is frequently associated with fronto-subcortical pathologies.

In conclusion, many studies show that cognitive dysfunction in early subcortical VaD includes retrieval memory impairment, as well as deficit in mental control, problem solving, set-shifting, conceptualisation, and concurrent manipulation of information, which encompass various aspects

of executive function commonly associated with the syndrome of "fronto-subcortical dementia" [8]. This constellation of neuropsychological impairments is very close to the cognitive syndrome proposed by Erkinjuntti et al. [11] for the diagnosis of subcortical VCI.

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Functional Transcranial Doppler in Stroke Risk

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Brain's high metabolic demand requires that cerebral blood vessels have a fine tune regulation of vascular resistance, controlling blood flow distribution. Two fast regulating principles of cerebral perfusion are well accepted: cerebral autoregulation maintains a stable cerebral blood flow for a wide range of systemic blood pressure variation, and cerebral neurovascular coupling adapts local cerebral blood flow to the metabolic needs and activity of the underlying cortex.

Transcranial Doppler (TCD) allows a continuous and non-invasive monitoring of cerebral blood flow velocities in the basal cerebral arteries, which change according to distal arterioles vasomotor variations. Functional TCD is a tool designed to measure the increase of local cerebral blood flow due to regional cortical neuronal activation, accomplished by the neurovascular coupling.

As endothelial dysfunction affects neurovascular coupling, it disturbs the dynamics of the evoked blood flow response to cortical activation, as assessed by functional TCD. Vascular risk factors, including age, diabetes and smoking habits, have been shown to interfere with neurovascular coupling.

Functional TCD can also be useful for evaluating presymptomatic and even prelesional subjects with genetic diseases afecting the endothelial function. Fabry disease patients, without prior history of stroke or transient ischemic attack, had disturbed neurovascular coupling in the visual cortex.

Interesting findings seem to show that cerebral blood flow regulation may reflect the neurological dysfunction caused by cerebral microvascular disease, namely associated with slow gait speed and risk of falls. A better understanding of the relationship between cerebral hemodynamics and structural changes in the aging brain is an essential step towards identifying preventive and therapeutic strategies for age related cerebrovascular disease.

Functional transcranial Doppler in stroke risk is a new cerebrovascular research area, as reflected by the few published articles related to this topic.

In this presentation some physiologic aspects of cerebrovascular hemodynamics will be firstly discussed, with a focus on neurovascular coupling. It will be shown how transcranial Doppler can study the neurovascular coupling, and finally how this functional transcranial Doppler is able to potentially evaluate stroke risk.

Physiologic considerations on cerebrovascular hemodynamics

The relatively small human brain, which represents around 2% of the body weight, consumes 20% of total body oxygen and claims 15% of the cardiac output, in order to maintain the necessary levels of metabolic activity of 3.5 ml.100 g brain-1.min-1 [1].

Furthermore, the brain has no energetic reserve, thus requiring a continuous blood flow during the whole cardiac cycle. A proof of this statement is the fact that a pathologic condition involving an intracranial pressure high enough to prevent blood from entering the skull during diastole results in brain death [3].

Another important issue is that the brain is surrounded by bone, and therefore the intracranial volume must be kept rather constant, with equilibrium of brain parenchyma, blood and cerebrospinal fluid volumes [25].

Brain's high metabolic demand and these volume-balance requirements imply that cerebral blood vessels have a fine tune regulation of vascular resistance, controlling blood flow distribution.

How does brain regulate vasoreactivity?

Brain circulatory physiology is not yet fully understood and competing theories about the modulating role of myogenic, neurogenic and metabolic mechanisms still exist.

Regardless of their biological realisation, two fast regulating principles of cerebral perfusion are well accepted: cerebral autoregulation and cerebral neurovascular coupling.

Cerebral autoregulation maintains a stable cerebral blood flow for a wide range of systemic

blood pressure (BP) variation, as long as the fluctuations remain within 50-150 mmHg mean blood pressure [13].

Cerebral neurovascular coupling adapts local cerebral blood flow in accordance to the metabolic needs and activity of the underlying cortex [8]. The neurovascular unit, composed by the neuron, the glia and the vessel, assures this interplay for an adequate local cerebral blood flow distribution.

It is assumed that the small arteriolar resistance vessels are the effector structures of both these physiologic mechanisms. Also, similar effectors were suggested because both mechanisms show almost identical response times [2].

How can Transcranial Doppler (TCD) evaluate cerebrovascular reactivity?

Transcranial Doppler (TCD) is a non-invasive ultrasonographic procedure that measures local blood flow velocity and direction of blood vessels in the proximal portions of large intracranial arteries.

Since its first development, described in 1982 by Rune Aaslid, transcranial Doppler has allowed a continuous and non-invasive monitoring of cerebral blood flow velocities in the basal cerebral arteries, through temporal bone "windows" [1]. Although TCD does not register directly CBF in the small vasoactive arteriolar system, but rather in the cerebral basal distribution arteries, distal arteriolar calibre variation in response to physiologic stimuli will induce flow variations on basal arteries, and therefore blood flow velocity. It could be argued that TCD measures CBF velocities and does not measure the CBF itself. Nevertheless, since flow is equal to the product of area and velocity, and calibre in insonated basal cerebral vessels remains constant with pressure changes of up to 20 mmHg, flow velocity changes correlate closely to flow changes. So, TCD allows continuous non-invasive monitoring of regional CBF variations, doing it with an excellent temporal resolution [2, 9, 19].

There are several ways to study vasomotricity of cerebral arterioles. With TCD we can evaluate the vasoreactive response inducing an increase in CO2 (either from breathing carbogen or through an apnea test), we can study the performance of cerebral autoregulation by analyzing the pressure-driven cerebrovascular adaptation (either to induced or spontaneous variations on arterial blood pressures), and we can study the neurovascular coupling by evaluating the reactive hyperemia to cortical activation.

Each of these evaluations can be relevant for stroke risk in different situations. For example, looking at the vasomotor response to an increase in CO2 can be important for studying cerebrovascular reserve in patients with carotid or intracranial stenosis: it allows assessing the risk of ischemia and identifying a group with high risk of recurrent stroke. This can help to make decisions regarding revascularization, when there is already an exhaustion of vasodilatation in the arterial territory of the proximal stenosis [20].

Looking at the performance of cerebral autoregulation in acute stroke can be very helpful if this allows adjusting the blood pressure, and investigations are ongoing on this topic [7, 14]. This adaptation can potentially reduce the risk of further ischemia when BP decreases or help preventing edema and hemorrhage when BP increases. The analysis of the cerebral evoked flow to cortical activation is important to evaluate the performance of the neurovascular coupling unit, both for neuronal and endothelial dysfunction, and also allows localizing some cortical functions, as in the laterality studies [10]. It can be useful for predicting stroke risk [4], and after stroke it might help in assessing changes in motor organization with rehabilitation. Functional brain imaging may assist in the selection of rehabilitation methods that best foster recovery [24].

Functional transcranial Doppler

Neurovascular coupling (NVC) ensures that blood flow is increased to meet the increased metabolic demands of the activated neurons. A mismatch between the demand and supply would result in relative hypoperfusion and brain dysfunction.

Functional TCD is a tool designed to measure the increase of local cerebral blood flow caused by regional cortical neuronal activation, accomplished by the neurovascular coupling. For this purpose, CBF velocity in the cerebral basal distribution artery related to the simulated cortex is monitored, and velocities in "rest" and while performing the task are compared [5]. It is important to find which duration of the stimulation is adequate to the stimulus, and also a resting phase long enough to allow the velocity to reach the basal levels. During the whole monitoring, marks should signal the beginning and the end of the stimulation phase, for posterior analysis.

One possible way of evaluating NVC consists in monitoring posterior cerebral artery during visual stimulation. The P2 segment of the posterior cerebral artery is a very good option to study NVC, because functionally it supplies mostly the visual cortex, so the low spatial resolution of the technique is not a limitation in this case. Thus, when monitoring P2, after asking the subject to make a normal task like reading a text, we can

see that with a short initial delay to stimulation, the flow velocity increases rapidly, overshoots and then stabilizes at a constant higher level compared to resting conditions. After being transformed into relative data to become independent from the insonation angle, the flow responses are evaluated conventionally by the maximal flow velocity increase. Nevertheless, some developments allowed a different approach for studying all the dynamic features of the evoked flow response, such as the initial time delay, the steepness of flow velocity increase, the overshoot, and the stabilization phase [15].

Functional transcranial Doppler and stroke risk

It is expected that endothelial dysfunction will affect the normal dynamic characteristics of the visual evoked blood flow, and it has been shown with functional transcranial Doppler that vascular risk factors interfere with NVC.

While age ranging from 10 – 60 years did not affect NVC in a functional transcranial Doppler (TCD) study with a visual stimulation task and monitoring posterior cerebral artery [17], another study involving young and old subjects that assessed NVC in the anterior and posterior cerebral arteries during visual and executive function tasks found that overall NVC seems to be altered with aging [21]. While the younger group showed task-specific flow activation in one territory at a time, the older group showed a generalized increase in blood flow in both the territories in response to both tasks suggesting generalization of cerebral activity to compensate for age related loss of region specific function. Similar generalization of cerebral activity was also reported with functional MRI during cognitive tasks in elderly people [6].

NVC also seems to be disturbed in the presence of other vascular risk factors. It was shown to be impaired in type 1 diabetic children [16] and in women with gestational diabetes versus non-pregnant and healthy pregnant women [18]. Impaired visually evoked flow velocity response was also found to be associated with chronic cigarette smoking in otherwise healthy, young subjects. The impaired cerebral vasodilatory mechanism together with atherosclerosis may influence stroke occurrence and outcome in chronic smokers [12].

Functional transcranial Doppler can also be useful for evaluating presymptomatic and even prelesional subjects with genetic diseases affecting the endothelial function. As cerebrovascular disease is known to progress asymptomatically in the early stages of Fabry disease, a cohort of patients from families with the classical phenotype were studied with functional transcranial Doppler. The authors concluded that Fabry disease patients of both genders, without prior history of stroke or transient ischemic attack, may have disturbed neurovascular coupling in the visual cortex, as well as decreased resting posterior cerebral artery BFV. These findings support the role of functional TCD, along with duplex ultrasound and MR techniques, in the evaluation of these patients, since early stages of disease [4].

Finally, interesting findings seem to show that cerebral blood flow regulation may reflect the neurological dysfunction caused by cerebral microvascular disease [22, 23]. Data from the MOBILIZE Boston study shows that changes in CBF velocity responses to an N-Back task to study the NVC was significantly associated with gait speed and that subjects with higher NVC were able to suppress the negative relationship between white matter hyperintensities and gait speed [23]. A better understanding of the relationship between cerebral hemodynamics and structural changes in the aging brain is an essential step towards identifying preventive and therapeutic strategies for age-related cerebrovascular disease.

In conclusion, functional transcranial Doppler allows gathering new information about neurovascular coupling, contributing to the evaluation of vascular risk even in pre-symptomatic subjects, which outlines its interest as a non-invasive tool for cerebral hemodynamics research.

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Vascular Dementia – Is There a Way to Prevent It?

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Key words:
Alzheimer's dementia, cognitive impairment, subclinical ultrsound markers, vascular dementia, vascular risk factors

Aging is often associated with some cognitive impairment. Greater population life expectancy is one explanation for increased incidence of cognitive impairment cases. A large number of people with cognitive impairment and dementia is becoming one of the most important medical and social problems worldwide. Therefore, prevention of cognitive impairment is an imperative. Dementia includes a heterogeneous group of disorders, the most common being Alzheimer's dementia (AD) and Vascular dementia (VD). Most cardiovascular risk factors, such as hypertension, diabetes mellitus, hypercholesterolemia, atrial fibrillation, and smoking are not exclusively risk factors for VD, but also for AD. Early changes in the blood vessel wall can be detected by early ultrasound screening methods which allow us to detect changes before the disease becomes clinically evident. Early disease detection enables in-time management, and studies have shown that careful control of vascular risk factors can postpone or even reverse disease progression.

The global aging of the population has lead to greater numbers of older people, owing to factors such as an increasing life expectancy and a decreasing birth rate. Aging is usually associated with cognitive changes, which may range from mild changes in cognitive function to more severe impairment causing dementia. The growth in the number of patients suffering from dementia is becoming a burden of constantly increasing importance to society. Although Alzheimer's disease is the most common cause of cognitive decline in the aged population, independant causes of cognitive dysfunction such as vascular disease, subclinical brain injury, silent brain infarction, and clinically overt stroke are important causes and contributors to cognitive dysfunction [1]. The overall prevalence of dementia in wealthy countries is 5% to 10% in populations aged >65 years. The prevalence of Alzheimer's disease (AD) doubles every 4.3 years, whereas the prevalence of vascular dementia (VaD) doubles every 5.3 years. Vascular cognitive impairment is strongly associated with age. In low-to-middle-income countries, the prevalence of dementia is lower than in wealthy countries but is still related to age. Incidence rates are variable, but age-related [1, 2].

Mild cognitive impairment (MCI) is a clinical state of mild but clearly abnormal memory loss, without significant impairment in daily activities. In many instances, both clinically and pathologically, MCI represents a prodromal stage of Alzheimer's disease (AD). Some studies have shown that the presence of MCI in older subjects, regardless of the definitions and criteria used, increases the risk for developing dementia [3, 4]. Because cerebrovascular disease can cause mild cognitive deficits that affect multiple cognitive functions, the term 'vascular' mild cognitive impairment (VaMCI) was proposed [5, 6]. Patients diagnosed with VaMCI are in transition towards Alzheimer's disease. [7] Vascular cognitive impairment (VCI) encompasses all cognitive disorders associated with cerebrovascular disease, from developed mild cognitive deficits to dementia. VCI is a syndrome with evidence of clinical stroke or subclinical vascular brain injury, and cognitive impairment affecting at least one cognitive domain. The most severe form of VCI is VaD (Table 1) [1].

Dementia is a clinical syndrome characterized by the impairment of cognitive functions, such as memory, language, praxis, recognition and executive function, with the loss of functional capacity [8]. Dementia may be caused by a heterogeneous group of disorders, the most common being Alzheimer's disease (AD) and vascular dementia (VaD). While cardiovascular risk factors, such as diabetes mellitus, hypertension, hypercholesterolemia, atrial fibrillation, and smoking, are particularly relevant in the development of VaD, they may also play a role in AD [9, 10, 11, 12, 13, 14]. Thus both conditions may represent different spectrums of cerebral vascular disease depending on the extent of microvascular changes [15]. An association between impaired function of cerebral microvessels and cognitive impairment in patients with mild to moderate AD was shown in a study by Silvestrini [16].

Because some cardiovascular risk factors are modifiable, investigating the mechanisms by which they contribute to AD pathology and

Table 1. Types of dementia.

Dementia
1. The diagnosis of dementia should be based on a decline in cognitive function from a prior baseline and a deficit in performance in 2 cognitive domains that are of sufficient severity to affect the subject's activities of daily living. 2. The diagnosis of dementia must be based on cognitive testing, and a minimum of 4 cognitive domains should be assessed: executive/attention, memory, language, and visuospatial functions. 3. The deficits in activities of daily living are independent of the motor/sensory sequelae of the vascular event.
Probable VaD
1. There is cognitive impairment and imaging evidence of cerebrovascular disease and: a. There is a clear temporal relationship between a vascular event (eg, clinical stroke) and onset of cognitive deficits, or b. There is a clear relationship in the severity and pattern of cognitive impairment and the presence of diffuse, subcortical cerebrovascular disease pathology (eg, as in CADASIL). 2. There is no history of gradually progressive cognitive deficits before or after the stroke that suggests the presence of a nonvascular neurodegenerative disorder.
Possible VaD
There is cognitive impairment and imaging evidence of cerebrovascular disease but 1. There is no clear relationship (temporal, severity, or cognitive pattern) between the vascular disease (eg, silent infarcts, subcortical small-vessel disease) and the cognitive impairment. 2. There is insufficient information for the diagnosis of VaD (eg, clinical symptoms suggest the presence of vascular disease, but noCT/MRI studies are available). 3. Severity of aphasia precludes proper cognitive assessment. However, patients with documented evidence of normal cognitive function (eg, annual cognitive evaluations) before the clinical event that caused aphasia could be classified as having probable VaD. 4. There is evidence of other neurodegenerative diseases or conditions in addition to cerebrovascular disease that may affect cognition, such as: a. A history of other neurodegenerative disorders (eg, Parkinson disease, progressive supranuclear palsy, dementia with Lewy bodies); b. The presence of Alzheimer disease biology is confirmed by biomarkers (eg, PET, CSF, amyloid ligands) or genetic studies (eg, PS1mutation); or c. A history of active cancer, psychiatric or metabolic disorders that may affect cognitive function.
VaMCI
1. VaMCI includes the 4 subtypes proposed for the classification of MCI: amnestic, amnestic plus other domains, nonamnestic single domain, and nonamnestic multiple domain. 2. The classification of VaMCI must be based on cognitive testing, and a minimum of 4 cognitive domains should be assessed: executive/attention, memory, language, and visuospatial functions. The classification should be based on an assumption of decline in cognitive function from a prior baseline and impairment in at least 1 cognitive domain. 3. Instrumental activities of daily living could be normal or mildly impaired, independent of the presence of motor/sensory symptoms.
Probable VaMCI
1. There is cognitive impairment and imaging evidence of cerebrovascular disease and: a. There is a clear temporal relationship between a vascular event (eg, clinical stroke) and onset of cognitive deficits, or b. There is a clear relationship in the severity and pattern of cognitive impairment and the presence of diffuse, subcortical cerebrovascular disease pathology (eg, as in CADASIL). 2. There is no history of gradually progressive cognitive deficits before or after the stroke that suggests the presence of a nonvascular neurodegenerative disorder.
Possible VaMCI
There is cognitive impairment and imaging evidence of cerebrovascular disease but: 1. There is no clear relationship (temporal, severity, or cognitive pattern) between the vascular disease (eg, silent infarcts, subcortical small-vessel disease) and onset of cognitive deficits. 2. There is insufficient information for the diagnosis of VaMCI (eg, clinical symptoms suggest the presence of vascular disease, but noCT/MRI studies are available). 3. Severity of aphasia precludes proper cognitive assessment. However, patients with documented evidence of normal cognitive function (eg, annual cognitive evaluations) before the clinical event that caused aphasia could be classified as having probable VaMCI. 4. There is evidence of other neurodegenerative diseases or conditions in addition to cerebrovascular disease that may affect cognition, such as: a. A history of other neurodegenerative disorders (eg, Parkinson disease, progressive supranuclear palsy, dementia with Lewy bodies); b. The presence of Alzheimer disease biology is confirmed by biomarkers (eg, PET, CSF, amyloid ligands) or genetic studies (eg, PS1mutation); or c. A history of active cancer or psychiatric or metabolic disorders that may affect cognitive function.
Unstable VaMCI
Subjects with the diagnosis of probable or possible VaMCI whose symptoms revert to normal should be classified as having „unstable VaMCI"

the manifestations of dementia may have implications for prevention. Also, lifestyle factors at a younger age, such as physical, cognitive and work activity, diet and mild to moderate alcohol consumption, may be protective against AD [17].

The diagnostic evaluation of dementia is complex, with various criteria applied. The clinical diagnosis depends on the definition of cognitive deficits and the differentiation between normal age-related changes and pathological conditions. Because the variability of cognitive function among the elderly is great, it is difficult to quantify precise normative limits in this population group. The clinical diagnosis of dementia should always take into account the individual's decline from the premorbid level of functioning. In addition to the difficulty in differentiating between early AD and normal aging, the distinction among the various dementing illnesses presents a diagnostic challenge.

The initial diagnostic approach to cognitive changes with age includes a clinical assessment and a neuropsychological evaluation [18]. Neuroradiological procedures may be of benefit in assessing early morphological changes and are usually based on computed tomography (CT) and magnetic resonance imaging (MRI) findings. Identification of early stages of microangiopathic-atherosclerotic changes of the small brain blood vessels can be assessed by means of neuroimaging techniques such as positron emission tomography (PET) and single photon emission CT (SPECT) of cerebral blood flow (CBF) are also useful, but often have limited clinical availability [19, 20, 21, 22]. Novel neurosonological methods utilizing sophisticated software, may also have a place in the assessment of cognitive impairment, with findings potentially appearing prior to structural and morphological changes in the brain.

Color Doppler Flow Imaging (CDFI) and functional Transcranial Doppler (fTCD) are the neurosonological methods most frequently used for the assessment of a patient's vascular status, and the information obtained is helpful in the diagnosis of various forms of dementia. CDFI may show evidence of impaired cerebral blood flow. Ultrasound parameters, intima-media thickness (IMT), circumferential arterial stiffness, resistance, and pulsatility indexes of the common carotid artery were found to be age-dependent. Thus, these parameters can be used to determine the actual vascular age of individuals [23, 17].

Neurosonological parameters that may be useful in the early stages of memory deficit and cognitive impairment include arterial stiffness, intima-media thickness, the measurement of cerebrovascular reactivity, and flow-mediated dilation, as well as the detection of microemboli in cerebral arteries (Table 2). Data from recent investiga-

Table 2.

ULTRASOUND METHOD	MEASUREMENT/ ASSESSMENT	DIAGNOSTIC VALUE
Transcranial Doppler (TCD)	Assessment of blood flow velocity, flow resistance, vasospasm, blood vessel stenosis or occlusion, of all cerebral arteries.	Shows evidence of impaired cerebral blood flow.
Functinal Transcranial Doppler (fTCD)	Measures cerebral blood flow velocity changes due to neural activation during cognitive tasks. Uses pulse-wave Doppler technology to record blood flow velocities in cerebral arteries.	Useful in assessment of cerebral lateralization during major brain functions (i.e. language, facial processing, etc.).
Transcranial Doppler (TCD) – emboli detection	Noninvasive ultrasound method of detecting the presence of circulating emboli.	Detection of emboli and their origin in intracranial vessels.
Color Doppler Flow Imaging (CDFI) – carotid arteries	Noninvasive assessment of morphology and hemodynamics of carotid arteries.	Evidence of impaired cerebral blood flow.
Color Doppler Flow Imaging (CDFI) – vertebral arteries	Noninvasive assessment of morphology and hemodynamics of vertebral arteries.	Evidence of impaired cerebral blood flow.
Arterial stiffness	General term for the elasticity (or compliance) of the arteries.	Indicator of atherosclerosis.
Intima-media thickness (IMT)	Measurement of the thickness of tunica intima and tunica media, the innermost two layers of the arterial wall.	Detection of atherosclerosis and, tracking the regression, arrest or progression of disease.
Pulse wave velocity (PWV)	The speed of travel of a pulse or energy wave that travels through the circulation	Shows evidence concerning the prognostic significance of large artery stiffening.
Flow mediated dilation (FMD)	Measurement of endothelial function by inducing reactive hyperemia by temporary arterial occlusion and measuring the resultant relative increase in blood vessel diameter by ultrasound	Non-invasive test for assessing endothelial function.

tions suggest that these parameters may be useful as markers for identifying patients with mild cognitive impairment who, as stated earlier, may be at greater risk for developing dementia [23].

Recently, a TCD study on cerebrovascular reactivity in VaD and AD patients, showed reduced flow velocity (FV) and increased PI with significant vasoreactivity reduction in both types of dementia, as indicative of impaired microvasculature compared to controls. There were no differences between the two types of dementia [24]. Although it is currently not possible to differentiate between the various types of dementia by means of TCD, the reproducibility and safety of this screening technique makes it potentially valuable in the diagnosis of dementia in the future.

Both AD and VaD changes are present in smaller vessels, where occlusion secondary to stenosis/thrombosis or spasm (which occurs as a reaction to an elevation in mean arterial pressure) results in elevated total peripheral resistance. These dementias may thus represent end-organ failure secondary to the effects of vascular disease [25]. Several years ago a study by Rundek et al. described the changes of CVMR in patients with VaD, and to a lesser extent in those with AD [26]. A reduction in CVMR was associated with cognitive decline at 12 months follow-up, as reported by Silvestrini [16]. These results suggest that vascular factors are important in the pathogenesis of cognitive impairment in some patients with AD. AD is characterized by various pathological processes, such as cerebral angiopathy, atherosclerosis, capillary endothelial and basement membrane changes, and thus the cerebral blood flow may be impaired. Changes of CVR in the absence of neck vessels stenosis may reflect increased arteriolar wall stiffness attributable to intrinsic anatomical changes.

Roher et al. have shown similar results. PI of the arteries in AD patients is generally greater than that of similarly aged patients without dementia. They suggest that with the increased artery wall rigidity imposed by atherosclerotic changes, mean flow velocities were generally lower in patients with AD [27].

Thus vascular status should be evaluated in all patients presenting with cognitive impairment. The possibility of influencing cerebral microvessel function by means of a more aggressive approach to the therapeutic control of vascular risk factors may have practical implications in the managment of AD [16].

Transcranial Doppler also has a place in detecting asymptomatic spontaneous cerebral emboli (ASCE) which are common findings in patients with VaD and AD [28]. One of the most common sources of ASCE is carotid artery disease. Embolic signals are often detected by TCD of the middle cerebral arteries when monitored for a number of hours in most patients with symptomatic and severe stenosis [29]. Results of large emboli are stroke and transient ischaemic attack, but repeated small asymptomatic emboli over a long period of time may cause progressive cerebral damage. During open heart surgery or carotid surgery microemboli entering the cerebral circulation might cause memory loss and cognitive impairment. [30, 31] Valvular heart disease, atrial fibrillation and paradoxal embolisation of venous emboli into the arterial circulation may also result in ASCE [32, 33].

Both intracranial and extracranial neurosonological methods are convenient, relatively widely available, and generally inexpensive diagnostic tools. Intracranial haemodynamics of the aging brain can sucesfully be assessed using TCD, functional TCD assessing the response to various stressors, and the TCD detection of cerebral emboli, while extracranial neurosonological methods involve the measurement of intima-media thickness (IMT), plaque formation and composition, and alterations in arterial mechanisms based on B mode ultrasound imaging, such as pulse pressure wave or flow-mediated dilation.

Vascular dementia is an important and often overlooked form of dementia. Data indicate that it may become the most common form of dementia in the elderly affected by ischemic heart disease and stroke. Most cases of vascular dementia present with a subcortical form of dementia with prominent executive dysfunction that often stays unrecognized by relatives or caregivers for a certain amout of time. Treatment may improve the prognosis of the condition, but primary prevention of vascular dementia is still the most effective cure, and it depends on early identification and appropriate control of vascular risk factors.

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Advances in Neurorehabilitation After Stroke

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Stroke is the leading cause of disability, and about 65% of stroke survivors experience long-term functional limitations. Despite great advances in acute stroke therapy – mainly by thrombolysis which had generated the acute stroke management (stroke units) – most of the patients remained disabled and need rehabilitation. Due to the international classification of functioning (ICF), the aim of the rehabilitation therapy is focused not only on functional recovery (which is often limited) but also to the reintegration of the patients in their former social life and work.

After stroke, nearly all patients are affected in a complex manner: motoric dysfunctions, restriction of upper extremity functionality, broad ranges of neuropsychological deficits, communication and swallowing problems, post-stroke depression etc. Each system has their own temporal development during the rehabilitation process (e.g. degeneration of the pyramidal tract, recovery, neuroendocrinological adaption). Thus, it is not simple to focus therapeutic management only on one aspect of the dysfunction. At least, the risk for complications such as aspiration, cardiovascular problems, diabetic control, fall with fractures, frozen shoulder and others are very high.

New insights in the effect of stroke lesions and therapeutic methods have changed traditional clinical rehabilitation and more evidence based therapies are provided. The rehabilitation process is divided in regeneration, neuroplasticity and adaption. Learning and repetitive exercises are the most important aspect for the rehabilitation success. In addition, neuronal aggregates adjacent to a lesion in the brain areas may take over the function previously played by the damaged neurons. Such reorganization modifies the interhemispheric networking in organization of the cortices. This reorganization may be responsible for clinical recovery of motor performances and sensorimotor integration after a stroke.

Current methods in stroke clinical rehabilitation

In the therapeutic decision making several issues are relevant for neurorehabilitation after stroke: 1. Primary and secondary prevention 2. Exercises by therapists (physiotherapy, ergotherapy, communication and swallowing, neuro-psychology 3. Support by special therapeutic tools (e.g. robotics, rTCS) and 4. Pharmacological intervention.

Prevention

The prevention of expected common complication is one of the important targets after stroke onset. Primary prevention should avoid typical complications in the early phase after stroke such as aspiration, joint luxation, decubitus, malnutrition, bladder infection, pulmonary embolism and trauma by falling. Secondary prevention is in accordance with the recommendation of secondary stroke prevention: treatment of hypertension, hypotension, diabetic control, lipids, cardiac control of rhythmic activity or antithrombotic therapy, vascular risk factor management.

Physiotherapy

The most used traditional therapeutic approaches are founded by Bobath which has failed in clinical trials to be more effective in comparison with unspecific approaches. Thus, the target agreements with patients in relation to ICF are improvement of physical fitness, balance and gait. Walking training improves walking capacity and self-care in different stages of stroke, but the training frequency should be high. However, the effects of training on death, dependence, and disability after stroke are unclear. There is evidence to incorporate cardiorespiratory training involving walking within post-stroke rehabilitation program to improve speed, tolerance, and independence during walking. For the treatment of pain coordination with physical and pharmacological therapies are recommended.

Upper Extremity

The improvement of sensomotoric affection of the hand and arm are difficult to realize by classic ergotherapy. Contrasting with the increase in performance due to spontaneous recovery, a concurrent decrease of spontaneous arm use has been supposed to occur following stroke. This decrease may be due both to the higher effort and attention required for successful use of the impaired hand and to the development

of learned nonuse in that the preference for the less affected arm is learned as a result of unsuccessful repeated attempts in using the affected arm. The constraint-induced therapy (CIT) protocol, which was proved in animal experimental settings, which forces the use of the affected limb by restraining the use of the less affected limb, has been specifically developed to reverse learned nonuse. CIT has been shown to be effective in the recovery of arm and hand functions after stroke in multisite randomized clinical trials. Other therapeutic strategies with circle training containing multiple functionalities are promising. The application of mirror is done to pretend the brain with a normalized illusion of motion of the paretic arm and hand. This supports the hypothesis of reconnecting brain areas.

Communication and swallowing

One of the most devastating consequences of stroke is aphasia. Communication problems after stroke can severely impair the patient's quality of life and make even simple everyday tasks challenging. One challenge is to predict the language outcome for stroke patients with aphasia. The new therapeutic approaches are based on non invasive focal electrical stimulation. The current review reveals that repetitive magnetic stimulation (rTMS) with or without conventional rehabilitation has positive effects on post-stroke aphasia.

In the early stroke phase swallowing is often and may be complicated by aspiration. Neuromuscular electrical stimulation (NMES) for treating dysphagia is a relatively new therapeutic method. There is a paucity of evidence about the use of NMES in patients with dysphagia caused by stroke. The majority of the reviewed studies describe some positive effects of the NMES on the neck musculature in the swallowing performance of poststroke dysphagic patients, especially when the intensity of the stimulus is adjusted at the sensory level or when the motor electrical stimulation is applied on the infrahyoid muscles during swallowing.

Neuropsychology

It is mandatory to check all stroke patients for basic cognitive function before rehabilitation. Memory or attentional deficits limit all rehabilitation processes. Thus the individual rehabilitation therapy design had to respect the neuropsychological test results.

Patients affected by right parietal lobe lesion can be severely impaired in sustained attention tasks, particularly in the left visual field or other modalities. For example, patients with right parietal stroke are commonly limited in their ability to attentionally track multiple moving objects in their left visual field when competing stimuli are simultaneously presented in the right visual field. There is discussion that post-stroke hyperactivity of the undamaged left hemisphere leads to excessive cross-hemispheric inhibition of the damaged right hemisphere, thus exacerbating the attentional deficits. The therapeutic strategies involved the compensation training but also medication (L-Dopa, amantadine).

Patients with attention deficits often suffered on circadian rhythmic disorders with inversion of day-night. Here, re-entrainment of the 24 hour rhythm may improve also the cognitive performance and thereby the rehabilitation effect. We have developed a specific therapy package (Attention lounge) including intense light application for the regaining of circadian rhythmic activity.

Special advanced Methods

Robotics

“Robot-mediated” post-stroke therapy is developed for the lower- und upper-extremity in the last decades. There is know clinical evidence that robotic interventions improve upper limb motor scores and strength. Most of the studies focus on training of the proximal arm for chronic stroke patients. Patients who receive electromechanical and robot-assisted arm training early after stroke are more likely to improve their generic activities of daily living. People who receive electromechanical-assisted gait training in combination with physiotherapy after stroke are more likely to achieve independent walking than people who receive gait training without these devices. Specifically, people in the first three months after stroke and those who are not able to walk seem to benefit most from this type of intervention.

rTMS / tDCS

In recent years, efforts have focused on investigating the neurophysiological changes that occur in the brain after stroke, and on developing novel strategies such as additional brain stimulation to enhance sensorimotor and cognitive recovery. Repetitive transcranial magnetic stimulation (rTMS) was introduced as a therapeutic tool for improving the efficacy of rehabilitation for recovery after stroke. The current hypothesis is that disturbances of interhemispheric activities after stroke result in a pathological hyperactivity of the intact hemisphere. The rationale of using rTMS as a complementary therapy is mainly to decrease the cortical excitability in regions that are presumed to hinder optimal recovery by low-frequency rTMS delivered to the unaffected hemi-

sphere, while high-frequency rTMS delivered to the affected hemisphere facilitates cortical excitability. There is a growing body of research in stroke patients investigating the effect of rTMS on facilitating recovery by modifying cortical and subcortical networks. Altogether, in combination with conventional therapeutic approaches, rTMS has a potential to become a complementary strategy to enhance stroke recovery by modulating the excitability of targeted brain areas. Today it is not clear which parameters (frequency, burst pattern, stimulation time etc) are optimizing the beneficial effects of rTMS on stroke recovery. Similar discussion are held in the literature about the effects of transcranial direct current stimulation (tDCS).

Pharmacology

One of the best studied effects on pharmacology improvement after stroke is the application of Botulinum toxin against the spasticity in the upper and recently shown also in the lower extremities. Also it is not so clear at which time during development of spasticity (very early, early, late) the application is most effective. International guidelines of neurological and rehabilitation societies recommend this treatment (level A). A very high portion of patients developed post stroke depression and several studies had demonstrated a positive effect of SSRI on the depression but also on the regaining of functionality. Motoric function is very often slowed down on both sides and the basal ganglia may be involved. Some clinical studies had demonstrated a positive effect of L-Dopa on the motoric and neuropsychological performance even in chronic lesions. Beyond that aspect and due to the high impact of cognitive performance, some discussion is held about the adjunct therapy by "neuroenhancer". Patients with cognitive dysfunction also present massive circadian rhythmic disorders which are negative for the rehabilitation. Some experimental and clinical data give a hint for the involvement of neuro - endocrinological disturbances. This would be very interesting because it would open more specific and known pharmacological treatment (melatonin, cortison, etc). To my mind to find the right "cocktail" will be one of the challenges for neurorehabilitation in the future.

Conclusion

Deepening knowledge of the mechanisms regulating the long-term recovery, observed for most neurologic sequelae after neural damage, might prompt newer and more efficacious therapeutic and rehabilitative strategies for stroke. Neurorehabilitation has the potential to be a fascinating part of clinical medicine.

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Brain Imaging in Neurorehabilitation

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Key words:
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This syllabus discusses the usefulness of navigated transcranial magnetic stimulation (TMS) as a brain imaging tool in stroke patients. TMS assessment of the motor tract function and walking ability over time in stroke patients with poor or non-existent initial gait is in the focus. Main data is derived from twenty-seven patients, first assessed one week post-stroke, and followed up for six months. Outcome measure in these patients was walking ability. Motor evoked potentials (MEP) in lower limbs early on predicted better physical functioning at 3 weeks and at 6 months in all patients ($p<0.05$). The value of MEP amplitudes and latencies in assessing the descending motor pathways in different stages of stroke recovery is discussed.

Stroke is one of the leading causes of adult disability in the developed countries. It is generally believed that the first weeks after the cerebral insult are crucial in determining the functional capacity of stroke patients. Functional recovery after stroke is attributable, at least in part, to the reorganization of the surviving brain elements [1]. It is known that immediate, targeted, and high-intensity therapy generally results in a better functional outcome than conventional treatment [2]. A number of studies have analysed the influence of the size or location of structural brain lesion on motor and behavioural outcomes. The size of the lesion is not the only determinant of the functional outcome; even minor damage in a critical part of corticospinal tract has been shown to limit patients' performance [3, 4]. Detailed understanding of the functional status of the remaining descending pathways might be one way to improve the prognostic accuracy and aid in developing targeted therapy.

Transcranial magnetic stimulation (TMS) represents a non-invasive tool to study directly the functional capacity of the motor pathway from cortex to the muscles. In stroke patients, studies with TMS have revealed smaller amplitudes and longer latencies of the motor evoked potential (MEP) elicited from the lesioned hemisphere when compared to those from the non-lesioned hemisphere. Most of the previous studies using TMS have analysed the hand motor cortex and lower limb studies are few [5].

Here I discuss data of 27 patients who fulfilled the TMS study inclusion criteria in the neurological examination within 10 days of stroke (inclusion criteria were: first supratentorial infarction or hemorrhagic stroke diagnosed by MRI, Modified Rankin Scale 0–2, Functional Ambulatory Category (FAC) 0–3, voluntary movement in the leg of the affected side, Barthel Index (BI) 25–75 points, no severe cognitive or communicative disorders, age 18 – 85 years). Patients were randomized to intensive gait-oriented rehabilitation (GOR) group or conventional therapy group (CT). None of the patients were independent walkers at the start of rehabilitation. Nineteen patients were not able to walk, two patients needed constant attention from one assistant in walking, three patients needed someone to provide balance support and three patients needed to have someone walking beside them. The demographic characteristics of the patients in the GOR (n=17) and CT groups (n=10) did not differ from each other (Table 1). GOR group was provided three weeks' in-patient rehabilitation in acute phase in order to enhance their motor abilities and help them regain their walking independence as soon as possible. Each patient spent a maximum of 1 hour/day in order to achieve 20 min actual walking either in the electromechanical gait trainer (Gait Trainer, Reha-Stim, Berlin, Germany) or on level ground. Each patient also received additional gait-oriented physiotherapy for 55 minutes daily. The patients in the CT group were most often transferred to a health centre after the first measurements. Later they visited the hospital on the test days. In the health care center, the patients had one therapy session daily, but not at comparable intensity as the GOR group. All patients were assessed with magnetic resonance imaging using a 1.5T scanner (Siemens Magnetom Avanto, Erlangen, Germany) with an 8-channel head coil. The MRI scan consisted of transaxial T2-weighted and diffusion-weighted images, coronal FLAIR and 3D T1-weighted images. The T1-weighted images were used for navigation during TMS. All MR images were evaluated by an experienced neuroradiologist and lesions were classified. White matter changes were graded according to the Fazekas scale. Lesions were

Table 1. Patient, lesion and physical functioning characteristics. Comparison of the gait-oriented rehabilitation (GOR) and conventional treatment (CT) groups at start.

Parameter	GOR	CT	p-value
Patients	17	10	NA
Age	64.5 (8.7)	69.5 (11.0)	0.203
Days since stroke	8.3 (2.0)	9.5 (1.9)	0.139
Gender, male/female	9/8	5/5	0.902
Lesioned hemisph, left/right	8/9	6/4	0.604
Lesion type, infar/ICH	11/6	8/2	0.537
Lesion size, mm	51.8 (26.9)	48.5 (18.0)	0.783
MEPs in TA, yes/no	6/11	3/7	0.824
FAC, category 0 - 5	12/1/2/2/0/0	7/1/1/1/0/0	0.975
MMAS, scores 0 – 48	20.5 (10.5)	15.3 (13.4)	0.270

P-values obtained using independent samples t-test, Mann-Whitney U-test or Kruskall-Wallis H-test. NA, not applicable; ICH; intracerebral hemorrhage; MEPs in TA, motor-evoked potentials elicited from affected tibialis anterior; yes/no; FAC, functional ambulatory category: 0=unable to walk or needs two assistants, 1=needs continuous support from someone while walking to shift weight or maintain balance, 2=needs continuous/ occasional support from someone while walking to maintain balance and coordination, 3=needs someone walking alongside to give confidence, none of the patients were in the more independent FAC categories 4 or 5; MMAS, Modified Motor Assessment Scale (scores 0 – 48).

highly variable in terms of size, location, aetiology and thus MRI signal properties. All were located either at the motor cortical areas or were related to leg pyramidal fibers.

TMS was performed to study functional motor tract integrity. It was done with on-line navigation (Nexstim Ltd, Helsinki, Finland) using the patient's own structural MR images. Single monophasic stimulation pulses were delivered with a Magstim Bistim (Magstim Company Ltd, Whitland, Wales, UK) via a figure-of-eight shaped 70 mm coil. During mapping of representation area of tibialis anterior muscle (TA), the coil was held tangential to the scalp and the direction of the induced electric field was perpendicular to the central sulcus. The non-lesioned hemisphere was stimulated first followed by stimulation of the lesioned hemisphere. To elicit a response in the target muscle, stimulation intensity was increased up to the maximum output of the stimulator, if necessary. The location of the stimulation that evoked the largest response in TA was chosen as the stimulation site. The resting motor threshold (MT, percentage of maximum output intensity of the stimulator) was determined as the lowest TMS intensity at which at least 4/10 stimuli resulted in an MEP of >100 μV. Five MEPs were collected at the stimulation intensity of 130% MT. In addition, five stimuli at the same intensity at the optimal site were delivered to elicit the silent period (SP) during weak voluntary isometric contraction of TA. During TMS, the activity in the muscle being studied was monitored on-line and recorded by continuous electromyography (EMG) (ME 6000, Mega Electronics LTD, Kuopio, Finland). The EMG signals were filtered (8-500 Hz), amplified and stored for off-line analyses. MEPs with peak-to-peak amplitude ≥100 μV were included in analysis, and amplitudes and latencies were measured for each MEP. The duration of SP was measured from the end of the preceding MEP until the first re-occurrence of voluntary activation. SPs with the longest and shortest durations were excluded from further analysis, and the mean SP was determined of the remaining three values. TMS responses at 3 weeks and 6 months follow-ups were normalized with the TMS response value at the start in the group comparisons.

Motor cortex excitability and physical functioning tests were performed at the start, at 3 weeks, and at 6 months' follow-up. Also several motor scale scores were performed. The anatomical locations of the lesions in all 27 patients varied extensively. While a minority were pure cortical (n=3, all frontal), many lesions included combinations of cortical and striatocapsular parenchyma (n=7). The remaining lesions were located deeper (n=17). In addition to the location of the main lesion, multicentric locations were observed in many cases. The lesion diameters ranged from 15 to 100 mm.

The maximum output from the stimulator was not sufficient to elicit a response in every patient. The motor threshold, MT, and the optimal stimulation sites of the TA representation area were definable at the start in 9 lesioned hemispheres and in 25 non-lesioned hemispheres. At 3 weeks, two

more patients produced TMS responses when the lesioned hemisphere was stimulated, one in each group. At 6 months, MEPs were elicitable in four more patients in GOR, but no further responses were obtained in CT. The lesion size influenced MT at the start (lesioned hemisphere TA MT r=0.837, p=0.005, n=9).

The walking ability of all of the patients was poor (median FAC GOR 0 and CT 0 (0 – 1.25) NS between groups). None of the motor ability scores differed between groups at start. When analysing only if the patient produced a response after stimulation of the lesioned hemisphere, those patients with MEPs had higher motor ability than patients without MEPs (MMAS mean 29.1 (±7 .3) vs. 13.3 (±9.8), p=0.001). Intensive post-stroke therapy in the form of gait training resulted in larger improvements in walking ability, in muscle force of the knee extensors and in overall motor function in the GOR group compared with the CT group. Significant group differences were obtained in ANOVA (FAC: interaction F (df 2)=5.559, p=0.007; MI knee: interaction F (df 2)=4.930, p=0.011; MMAS: interaction F (df 2)=68.931, p=0.02). Normalized TMS response values of patients in the GOR group and in the CT group were compared at 3 weeks and 6 months. There were differences in the amount of change between GOR and CT groups in the lesioned hemisphere. At 3 weeks, the MEP amplitude in the GOR group increased and it was higher than in the CT group (GOR vs. CT, p=0.03). At the 6 months follow-up, the MEP latency in the CT group lengthened whereas in the GOR group it remained unchanged (group difference p=0.04) and the MEP amplitude in the GOR group increased (group difference p=0.05). The amplitudes declined during follow-up because they were calculated relative to the start amplitudes. These earliest amplitudes represent the overexcitability in the motor cortex which is present acutely after stroke and these normalize by 6 months. MEP elicitability at the start indicated significant prognostic value for walking speed and distance at 6 months, i.e. for the 10-meter walk test in GOR (p=0.017), see Table 2.

The follow-up of the recovery process of stroke patients from the very acute stage onwards was performed using a multimodal approach including lesion characterization with MRI and neurophysiologic and physical functioning evaluations. The intervention group received intensive gait-oriented rehabilitation for 3 weeks whereas the patients in the control group followed the conventional treatment path. The focus of this study was on assessing the motor tract physiology after stroke. The conduction properties of the unimpaired descending motor pathways to the affected side muscles during the early stage of stroke predicted better physical functioning. Gait-oriented rehabilitation resulted in better motor tract function which was evidenced in more and higher amplitude MEPs and better physical functioning at follow-up compared to the corresponding values in those who had received conventional treatment. Neither anatomical locations of the lesions nor cortical involvement vs. primary involvement of the subcortical motor tracts showed any statistically significant correlations with the MTs, MEP latencies and amplitudes or SPs. Only the lesion size influenced the MT values of the TA muscle. This is in line with the evidence that functional recovery is more likely related to changes in distributed neuronal networks rather than functions or lesions in individual regions.

Table 2. Motor outcomes at three weeks and at six months according to the existing versus non-existing MEP response after stimulation of lesioned hemisphere at the beginning of study in patients with acute stroke who received gait-oriented rehabilitation, GOR, N=17.

		GOR No MEP	GOR Yes MEP
3 weeks	FAC	3 (11)	4.5 (6)
	6 min (m)	275 (7)	396 (6)*
	MMAS	30 (11)	42 (6)*
6 months	FAC	3 (11)	4.5 (6)
	6 min	277 (11)	435 (6)*
	MMAS	32 (11)	40 (6)*

It is well established in patients with stroke that MEPs from the lesioned hemisphere are smaller than those obtained from the non-lesioned hemisphere and smaller than those of age-matched healthy subjects [5]. In addition, an increase in the MEP amplitudes is accompanied by an improvement of clinical and functional scores. However, many of the earlier intervention studies concentrated on hand motor cortex. Only few randomized controlled intervention trials have established that intensive practice with the affected hand and arm for 3 to 6 hours/day for 2 weeks can result in increased number of active TMS sites compared to less intensive treatment or no treatment [6]. The enlarged motor representation in the lesioned hemisphere was shown to remain for up to 4 months in the follow-up period. In our previous clinical trial, the MEP amplitudes in the lesioned hemisphere increased after 2 weeks of intensive hand and arm exercise therapy [7]. Similar results were obtained e.g. by Koski et al. [8], who reported that MTs decreased after more training, whereas MEP amplitude and map size

increased after less extensive treatment. Our results of gait rehabilitation and TA MEPs confirm their conclusion that TMS is useful in both moderately affected and in more impaired patients as a physiological assay of treatment-induced plasticity and functional gains. There is evidence that neural reorganization can be enhanced by gait-oriented rehabilitation. These results support previous clinical studies of MEPs of the lower limb in predicting motor recovery and ambulation and correlations between MEPs and gait recovery after stroke [9].

In a treadmill training study of Forrester et al. [10], 3/11 patients walked on a treadmill 3 times per a week for 6 months. The MEP amplitudes increased in all 3 trained patients in the lesioned hemisphere, whereas MEPs decreased in 6/8 of their untrained counterparts. We obtained corresponding results in early acute stage of stroke. Only 3 weeks of intensive gait-oriented walking training resulted in increased MEP amplitudes in the affected leg. Four weeks of gait training at subacute stage has been shown to decrease the MT for TA in the lesioned hemisphere [11] and the map size for TA increased in both hemispheres, whereas the corresponding value for abductor hallucis increased only in the lesioned hemisphere. Furthermore, these changes in corticomotor excitability correlated with the functional improvement in the subacute stage [11]. During the acute stage of stroke, we observed that those patients with preserved motor tract function demonstrated existing MEPs at a mean of 8 days post-stroke and showed good prognostic value for predicting physical functioning after 3 weeks and at 6 months. Obtaining MEP values is more robust than a clinical examination because it provides an unambiguous result also in individuals who cannot perform clinical tests such as the 10-meter walk. More detailed TMS methods, such as studies of intracortical inhibition, and utilizing other techniques, e.g. tractography, already during patient selection could provide a deeper understanding of the critical parameters of good motor function recovery.

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Combining Electrical Stimulation Mediated by Iterative Learning Control with Movement Practice using Real Objects and Simulated Tasks for Post-Stroke Upper Extremity Rehabilitation

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Key words:
electrical stimulation, iterative learning control, rehabilitation, stroke, upper extremity

Objective: Task specific training and Electrical stimulation (ES) are techniques used in rehabilitation of the upper extremity post stroke. This study describes the feasibility of using a rehabilitation system that combines personalised, precisely controlled levels of ES to the anterior deltoid, triceps and finger and wrist extensors during goal-oriented activity utilising real objects from daily life.

Materials and Methods: Four chronic stroke participants undertook seventeen intervention sessions, each of one hour duration. During each session, participants performed goal-orientated tasks while Iterative learning control (ILC) updated the ES signal applied to each muscle group. The update was based on the difference between the ideal and actual movement in the previous attempt at the task, measured using Microsoft Kinect and PrimeSense sensors. The control system applied the minimum amount of ES required with a view to facilitating success at each given task while maximising voluntary effort.

Results: Preliminary results demonstrate that ES mediated by ILC resulted in a statistically significant improvement in range of movement in all four joint angles studied (shoulder flexion; elbow, wrist and index finger extension) over 17 intervention sessions. Additionally, participants required signficantly less extrinsic support for each task. The tasks and system is described and initial intervention data are reported.

Discussion: The feasibility of using this system for assisting upper limb movement has been demonstrated. A large scale pilot RCT is now required.

Annually 16 million first strokes occur globally, and 10.3 million people are estimated to survive [1]. As age is a substantial risk factor, the aging of the world population means that a growing number of people are at risk, with associated impacts on the individual, their carers and broader society. Arm dysfunction is a major consequence of stroke; only 41% of people with moderate to severe stroke and 71% with mild stroke regain dexterity [2], which affects performance in activities of daily living [3] and subsequently care. In 2009, stroke alone was estimated to cost the EU economy over €38 billion, of which 50% was due to direct health care costs, 22% was due to productivity losses and 28% was due to informal care costs of people with stroke [4].

Whilst the majority of any functional improvement is seen in the first six months following stroke, functional gains can be observed over several years [5, 6]. A recent review and meta-analysis highlighted that there is strong evidence for physical therapy interventions which include intensive, highly repetitive task-oriented and task-specific training in all phases post stroke [7]. This presents a major challenge to healthcare providers, and is driving the development of rehabilitation technology which can deliver this specific and intense rehabilitation without using additional resources. Technologies such as electromechanical and robot-assisted arm training have been demonstrated to improve activities of daily living and arm function (but not muscle strength) [8]. However few evidence based technologies are routinely used in clinical practice in the UK. Identified barriers which need to be overcome to facilitate translation include usability, knowledge, education, awareness and access to ATs as well as cost [9]. One of the technologies which shows promise in meeting some of these barriers is Electrical Stimulation (ES) which has a growing evidence base [10], demonstrating improvements in range of movement, strength and spasticity.

The effectiveness of ES is increased when ES is associated with voluntary drive. It is there-

fore important to carefully control ES in order to support the user's intended movement. ILC is an advanced control paradigm that operates by comparing movement data from a previous attempt at a task to an idealised reference trajectory for the same task. It sequentially adjusts the level of stimulation given to each muscle group with a view to achieving the required reference trajectory. This iterative process applies the minimum level of ES for task attainment while simultaneously encouraging voluntary contribution from the participant. Previous studies combining ES and ILC have demonstrated feasibility of using PayPals electrodes to deliver precisely controlled stimulation to the anterior deltoid, triceps and wrist extensors [11-13]. The GO-SAIL (goal-oriented stimulation assistance through iterative learning) system used in this study, is a multi-channel ES system for the upper extremity that precisely controls ES through advanced iterative learning control algorithms [14]. The technology employed in this study includes three important developments to that used in previous research:

1. An electrode array is located over the wrist and finger extensors to enable functional hand gestures to be performed.

2. A Primesense is used to measure hand and wrist joint angles, reducing set-up time and removing constraints associated with contact-based sensors (e.g. goniometers).

3. A touch table displays the tasks in an interactive manner.

The system directly trains goal-oriented activities and is able to provide greater assistance than in previous research by including an electrode array to support functional hand and wrist gestures. This is expected to lead to further reduction in upper limb motor impairments, as reflected by evidence that effects resulting from training are mostly restricted to the actually trained functions and activities [10]. To be useful in longer term self-management, technologies need to promote adherence through stimulating and motivating rehabilitation. The use of a touch table provides such an environment, and, when combined with inexpensive non-contact sensors (Kinect and Primesense), represent a significant step in the development of technology that is suitable for translation into the home environment.

The aim of this study is to test the feasibility of using the multi-channel ES system to precisely control ES applied to multiple muscle groups in the UE in combination with real and virtual tasks to facilitate functional motor recovery post-stroke. The rehabilitation system has been designed to facilitate recovery of UE motor control and function in chronic stroke participants.

Method

Participants

The inclusion criteria for participants were: i) aged 18 years old or over; ii) stroke causing hemiplegia of at least 6 months duration; iii) impaired upper limb that includes the inability to effectively extend the elbow in reaching and impaired opening and closing of the hand iv) ES produces movement through a functional range; v) able to comply with study protocol; vi) able to communicate effectively; vii) able to provide written informed consent. The exclusion criteria for participants were: i) any active device implant; ii) a metal implant in the affected upper limb; iii) uncontrolled epilepsy; iv) pregnancy and lactation; v) any serious or unstable medical, physical or psychological condition or cognitive impairment that would compromise the subject's safety or successful participation in the study; vi) requirement of an interpreter; vii) current participation in another study involving physical rehabilitation of the arm. Following ethical approval, to date, a total of 4 participants have been recruited to the trial.

The rehabilitation system

Pals Plus electrodes were applied to the anterior deltoid and triceps, whilst the 24 element electrode array was positioned over the finger and wrist extensors. Multi-channel ES was precisely applied to assist participants' completion of the movement tasks. The system was goal-orientated; tasks included holding an imitation loaf of bread with one hand whilst simulating a cutting task with the other, or moving soap or toothpaste to a different position on the representation of the bathroom sink displayed by the touch screen. The control scheme considered each task to be a general optimisation problem where the desired movement was specified in terms of kinematic variables. For example, the task of moving the soap, involved reaching a certain position in Cartesian space at a predetermined time, with constraints which influenced the posture adopted, and the speed and smoothness of the motion. Healthy participants' movements were used to identify the optimisation components. [24]. ILC iteratively solves the optimisation by learning from experimental data recorded on the previous attempts of the task, in such a way as to solve the optimisation and hence complete the task. Thus, the stimulation signal applied to each muscle group is updated on every trial. In the current system, this involves using kinematic, kinetic and stimulation signals, which are used in combination with an underlying bio-mechanical dynamic model of the arm [14, 15].

Fig. 1. *The components of the GO-SAIL system: (1) Microsoft Kinect® and Primesense sensors which provide kinematic data for the ILC algorithm; (2) virtual and real tasks displayed using touch table; (3) SaeboMAS® arm support; (4) FES and multiplexor hardware (5) surface electrode array on forearm.*

A schematic overview of the system can be seen in Figure 1. Participants sat on a perching stool in front of a touch table adjusted to their height and reach. Their arm was de-weighted according to individual need and task using a SaeboMAS® arm support (Saebo, Charlotte, USA). Electrodes were positioned on the anterior deltoid, triceps and an electrode array was used over the common extensor complex of the forearm. Joint angles of the shoulder, elbow and wrist were recorded using a Kinect® (Microsoft, Washington) and a PrimeSense (Apple Inc, California). Data from these sensors fed into the control algorithm hardware and software, which updated the ES control signals for each muscle group to provide enough ES to assist performance. The therapist used the operator monitor displaying the GO-SAIL graphical user interface to select appropriate tasks and monitor training. A safety override button could be used to terminate trials with immediate effect if required.

Intervention sessions

The participants repeatedly practiced functional tasks assisted by ES over 17, 1 hour intervention sessions, lasting between 6-8 weeks. Participants sat on the perching stool in front of the touch table, with their hemiplegic arm supported by the SaeboMAS® arm support. The support was adjusted to allow the participant to access a greater range of active or ES assisted movement without causing abnormal posture in the upper quadrant. The aim was for the participant's hand to rest easily on the table top (see Figure 1). Electrodes were placed on the anterior deltoid, triceps and wrist extensors, ES was applied and the movement pattern was checked. For the wrist array, an automated programme stimulated electrode elements within the array to identify the combination of electrode elements that produced the optimal wrist and index finger gestures required in the tasks. For comfort and safety, upper limit stimulation amplitudes were identified for all muscles, which would not be exceeded in the intervention. Parameters within the model of the arm were also identified.

During each task, joint angles, timings and error magnitudes between the participant's arm movement and the reference movement were recorded to provide a measure of accuracy for each muscle group for unassisted tasks (i.e., movements without ES) and assisted tasks.

Unassisted tasks: Four button pushing tasks (at 75% of reach at each of the four locations) and one light switch task (at 75% of reach at the highest location), were completed pre and post each session. These consisted of one trial only.

Assisted tasks: The intervention practice tasks were determined by the therapist according to clinical need, and designed to present an achievable challenge. The tasks began with the participant's hand placed on the touch table in front of

their shoulder (see Figure 2) and were typically repeated six times. Participants were instructed to always try to initiate the activity and try to move their arm to complete the task themselves. During each task, ES mediated by ILC, was applied to all three muscle groups. This facilitated the movement of the participant's arm over the six repetitions of the selected task. A custom graphical user interface was used by the therapist to perform the subsequent tests.

Task Design

Daily life tasks were chosen that utilised reach and manipulation across the workspace, and were sufficiently challenging but achievable by the participants (see Figure 2). Four background images were used on the touch table: a default image, a table, a bathroom sink and a chopping board. Tasks included reaching and grasping using real objects relevant to the image. There were 5 main tasks; closing a drawer, switching on a light switch, stabilising an object, button pressing and repositioning an object. As illustrated in Fig. 2, the light switch was located at two different heights (low and high) and there were four table-mounted positions in which the buttons could be located or objects repositioned both in the sagittal plane and towards the frontal plane (45° across body, 45° to the hemiplegic side or in line with the shoulder). The objects were placed at different percentages of arm length (60%, 75%, 80% and 90%) from the participant's glenohumeral joint (see Fig. 2). The table was positioned at a distance of 45% of arm length away from the glenohumeral joint and 35 cm below the arm when the arm was held 90° horizontal to the shoulder.

Level of Arm support used during FES-assisted tasks

The level of arm support remained the same for the unassisted tasks. For the assisted tasks however, the level of arm support was reduced following consistently successful performance, to encourage voluntary effort. This was monitored and recorded for each task completed.

FES-unassisted and FES-assisted performance

The time it took to complete a task (or until maximum effort was achieved), joint angles and task success (i.e. whether the task was successfully performed) were recorded for each trial. Unassisted tasks: participants completed five unassisted tasks (i.e. without the aid of FES): the four button pushing tasks (located at 60% or 80% of reach in line with the shoulder, or at 75% of reach, 45° to the left or right of the shoulder), and the high light switch task (located at 75% of reach and 115° of elevation) at the beginning and end of each session. The unassisted tasks consisted of one trial only. These data were used to map changes in these performance measures over time.

In addition, the tracking error (i.e. the mean difference between the measured joint angle signal and the desired reference trajectory) for each muscle group was calculated across the six repetitions of each assisted task to quantify the change in task performance elicited by ILC.

Statistical analysis

FES-Unassisted and FES-Assisted Performance and Level of Arm Support: changes in the FES-unassisted and FES-assisted perfomance, and level of arm support required across the sessions were analysed by calculating best-fit linear regression slopes of performance against session number collapsed across all participants. Significance was associated with a value of $p < 0.05$.

Results

The feasibility trial took place at the Faculty of Health Sciences, University of Southampton. Data

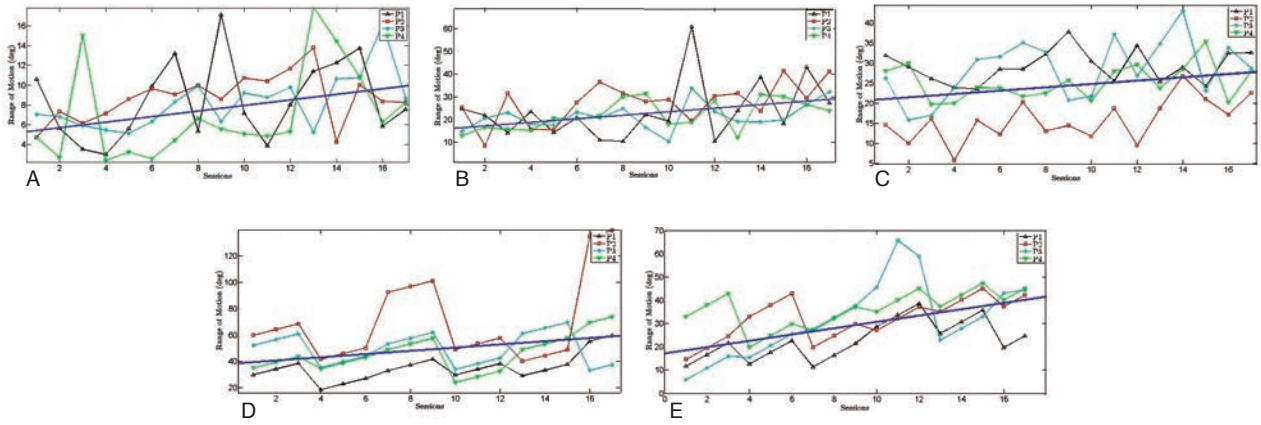

Fig. 2. *a) Changes in Range of Movement over the intervention a) High Light Switch Task: Shoulder Flexion b) Contralateral Task: Elbow Extension, c) Lateral Task: Elbow Extension, d) Near Reach Task: Wrist Extension, e) Far Reach Task: Index Finger Extension.*

Table 1. Regression slopes and p-values for range of movement in FES-unassisted tasks over the 17 sessions across all participants.

Joint angle	Task	slope	t-stat	p-value
Shoulder Flexion	High Light Switch	0.2814	5.6755	0.0054
Elbow Extension	Contralateral Reach	0.78	6.2702	0.0041
	Lateral Reach	0.4137	3.1752	0.0251
Wrist Extension	Near Reach	2.4521	2.8616	0.0322
Index Finger Extension	Far Reach	1.9814	2.7172	0.0364

are reported from four participants (3 male and 1 female, aged 44-55) who completed the trial over 6-8 weeks. They have all had a right cerebral vascular event causing left hemiplegia. None of the participants demonstrated any loss in sensation or passive range of movement. With gravitational support, participants had varying degrees of volitional proximal activity but all demonstrated an increasing deficit in activity distally.

The range of unassisted tasks during the intervention reflects different improvements in range of movement at the shoulder, elbow, wrist and index finger joints; the highlight switch demonstrated the most significant gain in shoulder flexion, the contralateral reach in elbow extension, the near reach in wrist extension and the far reach in index finger extension as seen in Table 1.

Analysis demonstrates that the intervention of ILC mediated ES in conjunction with the task practice successfully improved range of movement in the upper limb, at all joints over the intervention. Statistically significant mean range of movement improvements over the course of the intervention can be seen to be 5° in shoulder flexion (High Light Switch), 13° in elbow extension (Contralateral Reach), 42° in wrist extension (Near Reach), and 34° in index finger extension (Far Reach). Greater detail can be seen in Figure 2 which shows range of movement in each intervention session for each participant.

These results indicate reduced motor impairment. This will be further quantified with the clinical assessments post-intervention. Data collection is on-going.

Discussion

This study provides evidence of the feasibility of using the GO-SAIL system, incorporating ES mediated by ILC with real tasks for chronic stroke participants. The electrode array worked to enable hand gestures to be performed leading to changes in unassisted wrist and finger movement. No participants reported discomfort from the wrist array. The Primesense recorded hand and wrist joint angles, reducing set-up time and removing constraints associated with contact-based sensors (e.g. goniometers) and the touch table displayed the tasks in an interactive manner.

The results of this feasibility study are relevant to all studies in which non-contact movement measurement is required. This type of system will become increasingly important in the drive to deliver cost-effective improvements in stroke rehabilitation and to fulfil national clinical guidelines which include recommendations for patients to have every opportunity to practise within their capacity.

The results from this sample indicate reduced motor impairment following the intervention. The different improvements visible in Figure 2 relate to the movement requirements necessary for performing the different tasks. The ipsilateral and contralateral tasks challenged the elbow extension, but not the shoulder flexion. Participants were able to control their shoulder flexion and elbow extension so this may have reduced the degrees of freedom allowing the participants to forcus (focus) on their wrist extension. The far reach task challenged all joints, but was the only task to require index finger extension to complete the task; repetitive practice resulted in the most significant improvement in index finger extension. The highlight switch task challenged participants repeatedly in terms of their shoulder flexion, and this is where the changes in movement occurred.

In clinical practice,outcome measurements would generally be recorded in line with the WHO International Classification of Functioning, Disability and Health [16]. However clinical outcomes generally do not measure incremental changes in movements, but solely provide a pre-post perspective. It can be oberved from the graphs that although the trend is in an overall direction, the day to day fluctuations could mean that a pre-post measurement could present a misleading picture of what the participant is achieving. Additionally, feedback is known to be an important factor in rehabilitation, and this type of system could be used to provide feedback.

Nevertheless, despite observing an improvement in range of movement it was still evident

that further refinement of fine finger movement is required to optimise transfer of the benefits observed in to activities of daily living. Additionally, whilst the non contact technology worked well, it is still not at a stage where it could be easily transferred into people's homes. On-going refinements, however, mean that this can be expected within 5 years.

Limitations of the study were a small sample size, no control group or follow-up (due to time constraints). Participant had also taken part in previous ILC studies, so it is possible that the improvements seen were not representative of participants who have not had the opportunity of using ES mediated by ILC. Now we have demonstrated the feasibility of using this technology we will seek to verify these results with a larger sample of participants in a randomised controlled trial or cross-over study design in which the effects of no ES (unweighting from the arm support alone) or ES that is not precisely controlled by ILC are compared with ILC controlled ES. In addition further refinement of the hand movement is required.

Conclusion

This study aimed to assess the feasibility of using the innovative GO-SAIL ES system that uses advanced ILC algorithms to precisely control stimulation to the anterior deltoid, triceps, and wrist and finger extensors during task specific upper extremity training. The feasibility of the system has been demonstrated by supplementing activity and promoting the successful completion of a range of functional tasks.

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Hemiparetic Gait in Stroke Neurorehabilitation

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gait,
neurorehabilitation,
stroke

The restoration of gait after stroke is a primary and long-term goal of neurorehabilitation. This article focuses on the update scientific theories for the influence of neurorehabilitation on restoration of hemiparetic gait due to unilateral supratentorial stroke. At presence it is accepted that stroke patients have an optimal time window for fast recovery within the rehabilitation. A significant motor improvement can be achieved in the first 6 months after stoke following by a plateau, although some functional recovery may be observed many years after stroke. Gait restoration in chronic hemiparesis is mainly associated with the use of optimal behavior strategies for compensation the existed motor deficit where the non-affected, clinically healthy side is more involved. Recent concepts emphasize on optimal stimulation of brain plasticity using relevant task-oriented and high-intensity training in better motivated and moving patients who have preserved cognition and receive family support.

Since the impairment of gait is responsible for a long-term disability and handicap in many chronic stroke patient, the restoration of gait becomes a major goal in neurorehabilitation [24]. Approximately 65% of stroke survivors with initial motor deficits of the lower extremities show some degree of motor recovery. Predicting outcome on the basis of expected neurological and associated functional recovery helps for planning the appropriate neurorehabilitation [17].

This article is focused on the kinetic, footprint and electromyographic (EMG) gait patterns in hemiparetic walking following supratentorial stroke – the most common reason for permanent disability in stroke survivors.

Neurophysiology of gait

Normal gait

Normal human gait is a natural movement defined as bipedal and biphasic, forward propulsion of the center of gravity with minimal expenditure of energy during locomotion. It is a result from dynamic interactions between a central program and feedback mechanisms [12].

The basic motor patterns for stepping are generated in the spinal cord, where networks of nerve cells, named Central Pattern Generators (CPGs), generate movements and enclose information necessary to activate motor neurons in the suitable sequence for motor patterns. These "innate" networks have a capacity to generate intrinsic pattern of rhythmic activity independently of sensory inputs. The CPGs are under supraspinal control of walking that involves various brain regions, including cerebral motor cortex, cerebellum, and brain stem. Peripheral sensory information and descending inputs from motor cortex modulate continuously the CPGs function, the drive for locomotion and the coordination to negotiate a complex environment [13, 23].

Hemiparetic gait

Motor outcome after unilateral supratentorial stroke is known to depend on the location of the brain lesion and the total number of residual descending fibers in the cerebral peduncles [48]. Bilateral impairments and different diaschisis phenomena are observed in unilateral hemispheric lesions while the common course of restoration of motor function consists of a regular sequence following a general pattern of reflex changes and ability for voluntary movement [46]. A complex functional reorganization involving more or less clinically "healthy" side is related to motor recovery after stroke utilizing those residual descending motor pathways, which are unaffected by the lesion and are bilaterally organized [19, 33].

These findings suggest that motor behavior of chronic stroke patients reflects the complex relationship between morphological lesion at the onset of stroke and associated structural and functional brain reorganization that may result in a newly and bilaterally organized control of ambulation in the presence of motor deficit. The final motor output is generated from one side – by the preserved CPGs in the spinal cord, which are programmed to operate in a stereotyped manner under supraspinal motor control mechanisms, and from other side – reflect some newly and

bilaterally organised alternatives in the coordination between segmental and suprasegmental control, which continuously modulate the spinally generated motor output. These alternative control mechanisms are suggested to underly in the restoration of hemiparetic ambulation despite the severity of post-stroke damage of the corticospinal pathways [40].

Theoretical background of motor recovery

The neurobiological basis of recovery after stroke is based on the theory of brain plasticity [4, 27]. It remains not completely understood although many evidences have been accumulated that after stroke the brain can reorganize itself [10, 28]. Several mechanisms for functional recovery are assumed: (1) brain repair (restitution, i.e. the biological recovery of the damage area itself); (2) adaptive reorganization (recruitment of new additional neural networks that can activate the same final pathways) and/or (3) compensatory strategy (behavioral substitution, i.e. patients learn to compensate for their deficit).

At present there are strong indications that all these mechanisms are potentially involved in the recovery process after brain injury, however the ability of human adult brain to reorganize itself remains more or less restricted. Irrespective of the type and the amount of applied therapy certain biological processes, characterized as the "spontaneous neurological recovery", are supposedly responsible for the functional outcome after stroke. The final outcome has been shown to be determined within a limited time window during the acute phase of brain injury – if recovery is seen early after stroke onset, better outcomes may be expected six months later although motor recovery may continue over a period of years in some individuals with appropriate rehabilitation [17].

Knowledge for post-stroke neuroplasticity has been grown recently gleaned from both animal models and human populations. It has been demonstrated that behavioral experience is the most potent modulator of brain plasticity. Based on the quantity and quality of motor experience, the brain can be reshaped after injury in either adaptive or maladaptive ways. Many studies have demonstrated the neurophysiological and neuroanatomical changes triggered by motor experience, injury and interaction of these processes. Using new techniques novel perspectives take place in the injured brain, providing a real-time window into post-injury plasticity. These new approaches are likely to accelerate the pace of basic research, and provide a wealth of opportunities to translate basic principles into therapeutic methodologies [28].

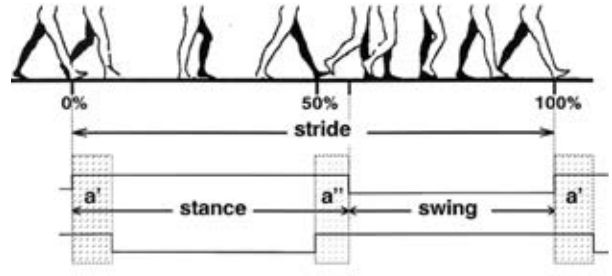

Fig. 1. *Courve of temporal variables of gait cycle. The gait phases are pointed in accordance to the right leg (up). The shadowed parts (a' and a'') reflect a total double support time [40].*

Gait variables

For assessment of gait various kinetics, kinematics and footprint variables are used.

Spatial and temporal gait variables

They give information about the kinetics of walking and can be measured by all gait methods. The important parameters are: gait velocity (cm/s), cadence (step/min), step length (cm), stride length (cm), cycle time (s), stance time (s), swing time (s), single and double support time (s) and the base of support (cm). Some systems calculate automatically functional scores for ambulation giving additional information for the overall gait performance (fig. 1) [1, 42, 49].

Footprint and footfall gait variables

Using walkway sensitive sensors it is possible to record the foot activated sensors and their time of activation/deactivation along with a dynamic pressure mapping of each footprint and footfall during normal and pathological walking (fig. 2) [40, 45].

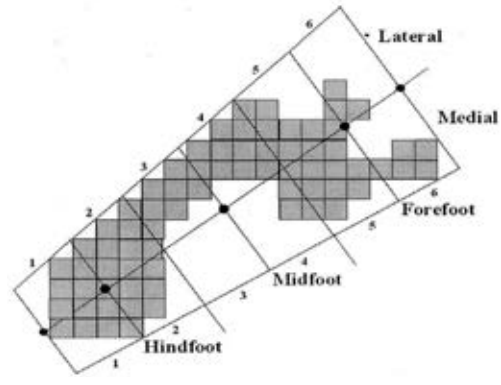

Fig. 2. *Footprint obtained by GaitRite® walkway. It is divided into 12 trapezoids, 6 for the lateral part and 6 for the medial part distributed into three segments: hindfoot, midfoot and forefoot. Each trapezoid, non-square, includes a specific number of sensors and the order for assigning sensor activation is heel-to-toe [43].*

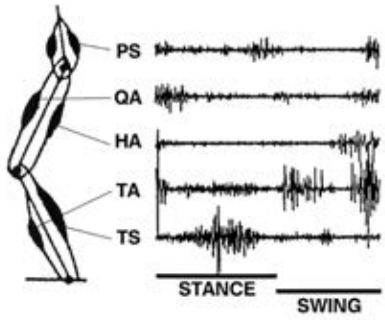

Fig. 3. *Location of EMG surface electrodes over paraspinal (PS), quadriceps (QA), hamstrings (HA), tibial anterior (TA) and triceps surae (TS) muscles. EMG pattern of normal walking [40].*

Polyelectromyography

Many studies used EMG records of muscle leg activity during walking by placing surface electrodes over paraspinal, quadriceps, hamstrings, tibial anterior and triceps surae muscles (fig. 3). Visual inspection, quantitative and qualitative analyses are used to identify reciprocal inhibition of antagonist muscles of ankle movement during walking cycle [40].

Gait patterns

Gait Patterns based on Spatial and Temporal Variables

Normal gait is characterised by a high symmetrical pattern in all spatial and temporal variables of any speed of walking [42, 49].

In chronic hemiparesis the gait shows a typical asymmetrical pattern regardless of the type and the side of stroke, more pronounced in slower walkers with severe disability using orthotic devices. The temporal gait variables change in a stereotyped manner (more quantitative than qualitative in nature) [12] – prolonged swing time on the affected side (AS) and prolonged stance time on the non-affected side (NS) were described in all post-stroke studies. The patients favored their non-affected leg in order to complete one stride of walking. They showed individual quantitative differences in gait kinetics in relation to the severity of stroke (fig. 4) [39].

Gait Patterns based on Footprint Analysis

It has been shown that the footprint patterns are relatively symmetrical in the phases of normal walking regardless of the velocity performance (fig. 5A) [42]. However, a significant gait asymmetry with prolonged footprint peak times on the NS and shorter times on the lateral footprint on the AS were found in post-stroke hemiparetic gait, more pronounced during slower walking. The patients chose their preferred walking velocity using stereotyped, alternative gait patterns where the contribution of the NS was larger than that of the AS especially in slower locomotion (fig. 5B). A high variability of the individual footfalls more pronounced on the AS was also described [44, 45]. The principal component analysis of the footprint peak times separated the hemiparetic stroke gait from the normal walking with a total predicted classification of 97.1% [44].

The changes in walking speed were found to produce quantitative alterations in the overall gait variables and to induce inverse changes in the temporal gait parameters, footprint and footfall peak times on both sides in patients and controls [1, 42, 45].

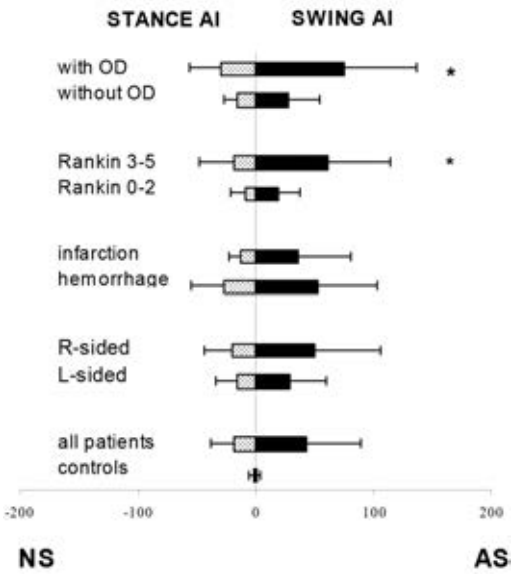

Fig. 4. *Gait asymmetry index (AI) in hemiparetic patients and controls [41].*

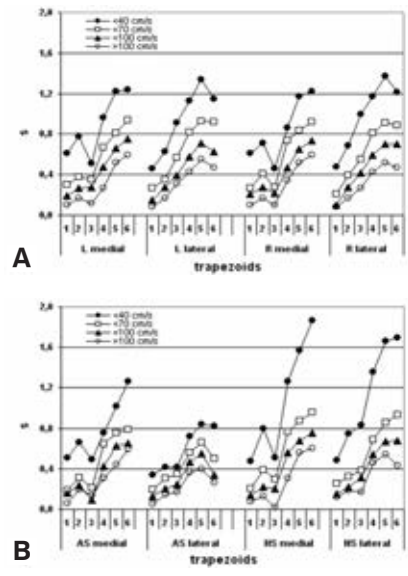

Fig. 5. *Footprint gait patterns in relation to walking speed in healthy **(A)** and hemiparetic stroke **(B)** subjects [44].*

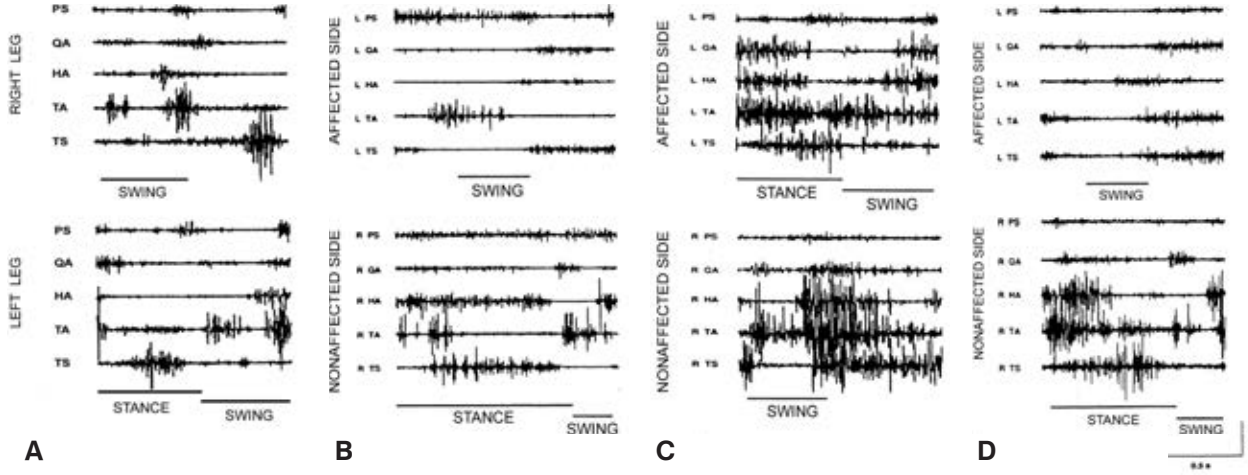

Fig. 6. *EMG patterns in normal* ***(A)*** *and hemiparetic gait* ***(B, C, D)*** *based on the reciprocal ankle TA/TS muscle inhibition.* ***A.*** *Normal gait with clear TA/TS reciprocity during swing and stance phases;* ***B.*** *Stroke gait type I – a prolonged swing phase with bilaterally preserved TA/TS reciprocity;* ***C.*** *Stroke gait type II – co-activation with bilateral TA/TS reciprocity during swing phase;* ***D.*** *Stroke gait type III – reduced EMG activity on the AS [40].*

Gait patterns based on EMG analysis

It has been demonstrated that healthy persons have nearly symmetrical and relatively consistent reciprocal patterns of EMG activities of lower extremities more expressed for distal muscles during walking – a reciprocal inhibition of antagonist (tibial and triceps surae) muscles during ankle movement is typical for all speeds of normal walking (fig. 6A) [40].

The patients with chronic hemiparesis use different strategies of reciprocal muscle activation and types of ankle movements depending on the severity of leg muscle paresis, the degree of gait recovery and the use of orthotic devices. A larch variability of EMG patterns during walking have been described by several studies – based on abnormal leg muscle activation [20], synergy exhibited by the NS [37], primitive patterns of mass extension and flexion [30], reciprocal ankle (TA/TS) muscle inhibition [40] and co-activation [22] – fig. 6 B, C, D. These findings confirm that the gait alterations after stroke affect both legs and the motor system contralateral to the brain lesion appear to be relatively disinhibited with co-activation significantly elicited during swing phase on the AS. Thus even in present of motor deficit both legs act in a co-operative manner, each limb affecting muscle activation and temporal behaviour of the other. Orthotic devices are common in cases with reduced distal motor outcome with severe peroneal muscle deficit where the ankle on the AS needs to be stabilized. However, in presence of motor deficit the relationship between gait performance and plantar flexor strength appered to be more complex and secondary to the brain reorganisation following stroke.

Gait Neurorehabilitation

Restoration of motor functions after stroke is a complex process involving spontaneous recovery and appropriate therapeutic interventions. Its primary goals are stroke patients to be able to walk independently and to manage to perform daily activities. Rehabilitation programs focus on gait training at sub-acute and chronic stroke patients where the rehabilitation outcome is strongly associated with cognitive function (attention, motor adaptation, learning and ability for re-learning), the degree of motivation and the engagement of the patient and his/her family [6].

The approaches used in gait rehabilitation after stroke include neurophysiological and motor learning techniques, robotic devices, Functional Electrical Stimulation (FES), and braincomputer interface (BCIs). The majority of methodologies applied are ***bottom-up*** (based on neural plasticity) and ***top-down*** (based on the state of the brain after stroke). There are general agreement that the combination of different rehabilitation strategies seems to be more effective than overground gait training alone [6]. However, the neurophysiological and motor learning techniques are not specifically focused on the gait rehabilitation. Compared to conventional therapy the use of robotic devices (including systems for BWSTT and FES) seems to be more effective for stroke gait recovery [6], but needs further evaluation.

The functionally orientated manual physical therapy aims to restore the preferred walking velocity and gait symmetry, however different degree of asymmetries in kinematic and kinetic variables of hemiparetic gait are often seen af-

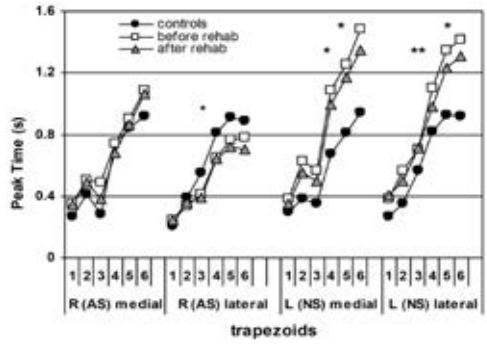

Fig. 7. *The footprint peak times of hemipateric patients before and after rehabilitation [43].*

ter rehabilitation. Most of the studies report for improved preferred walking speed as a result of rehabilitation with variations between the subtypes of stroke. As general, patients with better functional outcome (higher gait velocity, higher Barthel Index and more symmetry in swing and stance duration) at the start of rehabilitation obtained higher gait capability at the end of rehabilitation. However, it has been observed that in chronic post-stroke hemiparesis the 3-weeks intensive neurorehabilitation is effective to improve the kinetic gait performance but appears insufficient to change the central programming of gait footfall patterns [43, 45].

Gait Rehabilitation Techniques

Modern gait rehabilitation is based on physical therapy interventions with robotic approaches and aims to improve functional ambulation after stroke. According to the Cochrane review the classic neurological gait rehabilitation techniques can be classified in two main categories: neurophysiological and motor learning [6, 25].

Neurophysiological techniques

They are based on the theories that the physiotherapist supports the correct patient's movement patterns, acting as problem solver and decision maker with the patient being a relatively passive recipient [43]. Commonly used in gait rehabilitation are:

Bobath concept – it is the most widely accepted treatment in Europe. The method consists on trying to inhibit muscle spasticity by passive mobilization associated with tactile and proprioceptive stimuli [7, 29].

The Brunnström method – it enhances the synergic pattern of movement developed during recovery from hemiplegia and encourages development of voluntary movement through reflex facilitation and sensory stimulation [8].

Proprioceptive neuromuscular facilitation (PNF) – through the application of a variety of stimuli (visual, auditory, proprioceptive et al.) it aims to achieve normalized movements and increasing recruitments of additional motor units maximising the motor response required [36].

The Vojta method – it is based on central pattern generator theories for postural and gait control and aims to activate the "innate", stored movement patterns in children with birth related brain damage and adult stroke patients [47].

The Rood technique – it focuses on the sequence of recovery and the use of peripheral (sensory) input to facilitate as much as possible the normal movement and postural responses [35].

The Johnstone method – it assumes that the pathological reflexes can be controlled through positioning and splinting to inhibit abnormal patterns and controlling tone in order to restore central control [16].

Motor learning techniques

Opposite to the passive role of patients implied in neurophysiological techniques, the motor learning methods aim to stress active patient involvement and collaboration in neurorehabilitation [6]. The task-specific and context-specific training is recommended to be relevant for the needs of patients including the additional training in the patient's own environment. The common motor learning approaches are:

The Perfetti method – it is a sensory motor technique developed originally for controlling spasticity in arms and subsequently – for improving gait. The rehabilitation starts with tactile recognition of different stimuli and evolves trough passive exploitation and manipulation of muscles and joints to active manipulation. It needs a certain degree of cognitive preservation to allow patient's cooperation [31].

Carr and Shepherd motor relearning method – it is based on the hypothesis that neurological patients learn in the same way as healthy subjects and through appropriate sensory inputs it is possible to modulate motor responses to a task. The rehabilitation protocol is initially focussed on movement that cannot be performed, followed by functional tasks and generalization of the training into activities of daily living [9].

Conductive education or Peto method – the rehabilitation protocols are focused on coping with disability in daily life of the patients by teaching them to use appropriate strategies [18].

The Affolter method – the incoming information is compared with past experience ("assimilation") which leads to anticipatory behavior [2].

Sensory integration or Ayres method [3] – the exercises are based on sensory feedback

and repetition which are seen as important principles of motor learning.

According to the only available Cochrane review on gait rehabilitation techniques there is insufficient evidence to determine if any rehabilitation approach is more effective in promoting functional recovery of lower limbs after stroke. Some studies reveal that patients receiving conventional functional treatment regimens need less time to achieve their functional goals compared to specific neurological approaches, such as Bobath [11]. There is strong evidence that patients benefit from task-oriented and high-intensity training to improve gait and gait-related activities after stroke supporting the view that functional recovery is driven mainly by adaptive strategies that compensate for impaired body functions [27].

There is no systematic review addressed to the efficacy of gait training methods in stroke rehabilitation. For acute stage of stroke there is a consensus that ground gait training helps for recovery of patients who cannot walk independently [5], but the opinion of gait training in chronic patients with permanent mobility deficits is contraversal – from negative to small, time-limited benefits mainly for walking speed [38]. Better results are considered in combination of ground gait training with treadmill or high-technology approaches (body weight support treadmill training, robotic devices, ect) [14, 26].

Robotic devices

Gait robotic devices (treadmill with body weight support, gait trainer and electromechanical exoskeletons) are related mainly to motor re-learning programs and promote learning depended on the self-selected usage and self initiated movements. They provide safe, intensive and task-oriented rehabilitation to people with mild to severe motor impairments after neurologic injury [15]. Their main advantages are associated with ability to increase the intensity of therapy under on-line control of kinetic and kinematic variables of walking, ability for repetition and increased training motivation through the use of interactive feedback along with reduction of the amount of required physical assistance that reduces the health care costs [6]. The positive effect of retraining gait with robotic devices on recovery of ambulation has been confirmed by several studies. However, according to recent Cochrane review robotic gait rehabilitation increases the walking independently mainly in patients with subacute stroke but not in patients with chronic stroke [25].

Functional Electrical Stimulation

Functional Electrical Stimulation (FES) has been used in rehabilitation of chronic hemiplegia since the 1960s. It consists on delivering an electric current through electrodes to the muscles that generates muscle contractions [34]. FES can be applied alone or as a part of a Neuro-robot.

Both robotic devices and FES can be controlled or triggered by biological signals recorded from the patient. Such positive feedback loop can enhance learning. The new approaches as brain-computer interfacing (BCI) and Functional near infrared spectroscopy-based BCIs are under investigations [6]. Repetitive Transcranial Magnetic Stimulation (rTMS) is applied to enhance motor recovery by a non-invasive deep brain stimulation of motor cortex.

Predictors of hemiparetic gait recovery

Knowledge for predictors of gait recovery after stroke can contribute to more appropriate selection of the rehabilitation strategy when different techniques in gait training are considered. Most of the studies confirm the significant association of recovery with younger age, better functional outcome (higher preferred gait velocity, Barthel Index and more gait symmetry at the start of rehabilitation), severity of stroke and brain ability for neuroplasticity (location and extent of damange, activation of secondary and contralateral areas, individual genetic abilities for brain reorganization) and better motivated and moving patients [6, 21, 32].

The individual variability on the final motor outcome among the patients suggests the important role of the natural post-stroke recovery combined with therapeutic intervention and the personal human ability for functional brain reorganization. Thus, the accurate predictive models for walking recovery remain elusive as many factors (external and internal) may influence this process.

Gait indicators for brain reorganization after stroke

Some recent studies have shown possible gait indicators for bilateral brain reorganization in chronic hemiparesis due to stroke. They are related to:

(1) the use of alternative kinetic and pressure-sensor footprint and footfall patterns where the non-affected side contributes more than the affected side [44, 45];

(2) stereotyped manner of changes in gait asymmetry depending on the contribution of the NS, the degree of motor control disability, the achieved preferred gait velocity and the use of orthotic devices [12, 39, 41];

(3) preserved gait asymmetry and higher variability in footfall gait variables after 3-week neu-

rorehabilitation despite its positive effect on the walking velocity, temporal and spatial hemiparetic gait variables [39, 45].

In a given chronic motor deficit all these indicators are possible to be quantitatively and qualitatively evaluated, analyzed and documented using a detailed kinetic, footprint and footfall expertise [45].

Conclusion

The restoration of gait after stroke is a primary and long-term goal of neurorehabilitation. It can be achieved by stimulating brain plasticity using relevant task-oriented and high-intensity training in better motivated and moving patients who have preserved cognition and received family support.

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Ultrasound Study of Intracranial Stenoses: Pre- and Post- Endovascular Treatment

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Key words:
atherosclerosis, endovascular treatment, hemodynamic effects, intracranial stenosis, ultrasound

Intracranial atherosclerotic stenosis (ICAS) represents a major cause of ischemic stroke in the world. Its incidence varies by ethnicity being highest among Asians and still underestimated in Caucasians. ICAS is held as a malignant cause of stroke with a very high stroke recurrence rate, highest for 70-99% stenosis and during the first 2-3 weeks after the initial event.

A systematic assessment of intracranial vessels by ultrasound is useful in diagnosing stroke patients with intracranial stenosis, understanding the nature of the stenosis, identifying ICAS patients at a higher risk of stroke recurrence. In fact ultrasound can provide real-time flow information (grade of stenosis, collaterals), study hemodynamic changes with time (regression/progression/stability of stenosis) or in response to various stimuli including breath-holding index to induce or augment a steal, and it can also detect transient emboli. All the information gathered by ultrasound has immediate therapeutic implications: anticoagulants for a partially recanalized embolus, calcium channel blockers for vasospasm, antiplatelet agents for dissection, immunosuppressants for vasculitis, intensive risk factor management and dual antiplatelet treatment for ICAS. In patients with recurrent symptoms despite best medical therapy, ultrasound can detect a progression of the stenosis, check for a possible increase of the embolic count downstream, assess intracranial arterial hemodynamics changes postoperatively (angioplasty alone or combined with new stents). In the latter cases, when verifying treatment efficacy, it is important to know the effects of a stent on cerebral blood flow in order to avoid misdiagnosis.

The aim of this lecture is to give an overview of the clinical applications of ultrasound in the assessment of intracranial stenoses in order to improve outcome and abate stroke risk.

Intracranial artery stenosis is a frequent finding in stroke patients, in particular intracranial atherosclerotic stenosis (ICAS) represents a major cause of ischemic stroke in the world. Its incidence varies by ethnicity being highest among Asians (30-50%) and still underestimated in Caucasians. ICAS is considered a malignant cause of stroke due to a very high stroke recurrence rate: highest rate for 70-99% stenosis and during the first 2-3 weeks after the initial event.

Important data on the intracranial circulation can be collected by Transcranial Doppler (TCD) or Transcranial color-coded duplex sonography (TCCS) through regions of the skull where the bone is naturally thin named bone windows; the main windows are the transtemporal, the transforaminal and the submandibular. The patency of the bone windows depends on several factors: bone thickness, patient age, gender, race and brain parenchyma. A thicker bone, old age, female gender, black race and brain atrophy make examinations more difficult. In these cases the signal can be enhanced by using ultrasound contrast agents. The most important characteristics that need to be recorded from each arterial segment are: blood flow direction, velocities (peak systolic, end-diastolic, mean) and pulsatility index (PI). PI is a marker of cerebrovascular resistance resulting from intracranial arterial stiffness and cardiac output parameters; it can be calculated using the following ratio: (peak systolic velocity)-(end diastolic velocity)/mean flow velocity. An increased PI represents enhanced cerebrovascular resistance.

No matter how the information is gathered (TCD or TCCS), the ability to interpret correctly vessel spectrograms is of paramount importance for understanding the neurovascular status of the patient. It must also be remembered that interpretation of ultrasound waveforms depends on the quality of the study performed, therefore appropriate training and equipment are essential. Often, we are confronted with patients having findings outside the classical schemes (i.e. bilateral disease, tandem lesions, coexistence of systemic and focal abnormalities) and this represents the real challenge of cerebrovascular ultrasound interpretation.

Stroke is a dynamic disease, consequently static neuroimaging studies (CT, MRI) characterize this process only partially; ultrasound monitoring in parallel with clinical evaluation offer in-

valuable information on the pathophysiology of stroke allowing for tailored treatment. Intracranial occlusion can be directly or indirectly detected by ultrasound. Direct criteria for proximal occlusion include no flow signal (TIBI 0) and minimal flow signal (TIBI 1), while blunted flow signal (TIBI 2) and dampened flow signal (TIBI 3) are criteria for distal occlusion. Indirect criteria of intracranial arterial occlusion comprise high resistance in the feeding vessel or in the proximal segment of the occluded vessel, flow diversion and signs of collateralization. Analogously to intracranial occlusion, intracranial stenosis criteria are direct and indirect. Direct criteria include progressive focal increase of blood flow velocities in ≥ 50% stenosis or paradoxical velocity decrease with very severe stenosis, near-occlusion or diffuse intracranial disease. Indirect criteria, which are present only in very severe stenosis (>80%), are the same as for occlusion: high resistance in the feeding vessel or in the proximal segment of the stenotic vessel, flow diversion and signs of collateralization. While transcranial ultrasound has very high specificity, sensitivity and negative predictive value, it has only modest positive predictive value, thus requiring confirmation by other imaging modality such as CTA or conventional cerebral angiography.

Once the anatomical diagnosis of an intracranial stenosis is made, it is crucial to understand the functional significance and the hemodynamic effects of the stenosis. Transcranial ultrasound can surely help by studying collaterals, testing for vasomotor reactivity and detecting emboli. In fact TCD/TCCS can provide real-time information on collateral flow and in case of vessel obstruction, activation of collateral pathways is very important for the clinical outcome of the patient. A complete circle of Willis and the possibility to activate primary collaterals (anterior communicating artery, posterior communicating artery) or secondary collaterals (ophthalmic artery, leptomeningeal arteries) reduces the risk of hemodynamic ischemic stroke. Sometimes we see a compensatory increase of blood flow velocity in the donor vessel due to recruitment of collaterals by vasodilation in tissues with compromised perfusion. This is called flow diversion and represents a natural steal by vessels distal to an arterial occlusion.

TCD/TCCS provides also information on hemodynamic changes in response to various stimuli (apnea, acetazolamide): if there is no velocity increase during apnea, we speak of impaired vasomotor reactivity (VMR) which translates into a higher risk of hemodynamic stroke. Sometimes we observe an intracranial steal, that is a paradoxical velocity decrease in the affected vessel and simultaneous velocity increase in normal vessels, in response to vasodilatory stimuli. This represents the "reversed" Robin Hood principle (i.e. rob the poor to feed the rich). Thus, when a pressure gradient favors the normally perfused brain parenchyma, a collateral vessel, which normally acts with a compensatory mechanism delivering sufficient supplies, can become deleterious for the patient by further depriving brain regions at risk of supply. If the steal is causing a clinical deterioration we speak of Reversed Robin Hood Syndrome, which is associated with a higher stroke recurrence rate.

Transcranial ultrasound is the only diagnostic method that can detect clinically silent emboli; this requires continuous monitoring of the major intracranial arteries and according to the current consensus the duration of the monitoring should be at least one hour. Microembolic signal (MES) detection identifies patients who are at higher risk of atheroembolic stroke, thus allowing to select those patients who could benefit from a more aggressive treatment. MES are also valid surrogate markers for verifying antithrombotic efficacy and a key for individualized stroke medicine.

Once the anatomical and functional diagnosis of an intracranial stenosis is made, it is crucial to understand the nature of the stenotic lesion. The differential diagnosis includes atherosclerotic disease, a partially recanalized embolus/thrombus, arterial dissection, vasculitis, vasospasm. Intracranial stenosis can be a dynamic process and serial examinations by TCD/TCCS can help understanding its nature; in fact cerebral artery stenoses may undergo progression (usually a plaque), regression (embolus, dissection, vasospasm, vasculitis), or remain stable during follow-up.

Intracranial artery stenosis is assumed to represent atherosclerotic plaque when no other obvious disorder, like vasculitis or dissection, is found on diagnostic work-up. However, we know relatively little about the composition of these cerebral artery stenoses apparent on noninvasive and invasive imaging studies. Another limit is that ultrasound detection of hemodynamically relevant intracranial stenosis limits the search to the advanced stages of the disease. In fact, intracranial stenosis represents only the most advanced stage of intracranial atherosclerosis, because the vessel maintains the same lumen diameter up to 40-50% stenosis due to the remodeling of the arterial wall according to Glagov regardless of the progressing atherosclerotic process. When this compensatory mechanism fails, a vessel stenosis develops.

All the information obtained on the nature of the intracranial stenosis will have immediate therapeutic implications: anticoagulants for a partially recanalized embolus of cardiac origin, cal-

cium channel blockers for vasospasm, antiplatelet agents for dissection, immunosuppressants for vasculitis, intensive risk factor management and dual antiplatelet treatment for ICAS. In patients with recurrent symptoms despite best medical therapy, ultrasound can detect a possible progression of the stenosis, exclude a branch occlusion, check for a possible increase of the embolic count downstream. The SAMMPRIS study has shown that early aggressive medical therapy is better than stenting for prevention of recurrent stroke. Nevertheless, there are subgroups of patients who remain at high risk of stroke despite aggressive medical therapy. In these patients, angioplasty alone or in combination with new stent types might still be an option, and transcranial ultrasound can quickly assess vessel patency by recording intracranial arterial hemodynamics changes post-operatively. In particular, due to the metal composition of the stent, TCCS can clearly display the stent, thereby determining the location and shape of it. When the treatment is effective, there is a significant and immediate decrease of blood flow velocities; after about a week, owing to the reshaping of the stent and vascular remodeling, there is a further improvement in hemodynamics with velocity values declining toward normal. A regular follow-up of these patients is advisable in order to confirm the efficacy of stenting and to detect residual stenosis or in-stent restenosis. Finally, it is important to underline that blood flow velocities in a stented vessel are higher compared to a non-stented vessel; consequently, when verifying treatment efficacy this has to be taken into account to avoid overestimation of residual stenosis or misdiagnosis of in-stent restenosis. Overall transcranial ultrasound provides accurate information on cerebral hemodynamics and represents the ideal modality for following disease progression and therapeutic effects.

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Sonothrombolysis

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Key words:
sonothrombolysis, ultrasound

Sonothrombolysis (ST) can increase the penetration of circulating tPA into the thrombus, promote the breaking and cleaving of the fibrin polymers, and improve the binding affinity of tPA to fibrin. A recent Cochrane Review of all the randomized studies published on ST reported significantly more recanalizations and better clinical outcome, with no effect on mortality. Two ongoing multicenter studies are verifying the efficacy and safety of ST in acute ischemic stroke. In both studies, endpoints will be clinical and sonological. ST is a promising tool for ischemic stroke treatment. Ongoing studies will provide us further data to be added to previous study and basis for more efforts in this promising direction.

Stroke is the first cause of disability and the second cause of death in the world. Ischemic stroke (IS) represents 80% of all strokes, and it is presently the most treatable one. In fact, in recent years, the spread of stroke units and the advent (appearance) of specific diagnostic tools and treatments have changed considerably the attitude towards active intervention in the acute management of stroke.

Intravenous recombinant tissue Plasminogen Activator (r-tPA) is the main medical therapy of IS, within a time window of 4.5 hours from symptom onset to thrombolysis,and possibly up to 6 hours in selected patients [1, 2, 3]. The mechanism of tPA is to favor arterial recanalization, thus achieving early reperfusion. The efficacy depends upon time window (the earlier the better) and location of thrombus (larger and more proximal thrombi are less prone to be lysed by tPA).

The thrombolytic drugs can be administered intravenously and/or locally, although there is no evidence of a greater efficacy with local administration [4, 5, 6]; moreover, intra-arterial tPA requires a complex, active and specialized organization.

Despite its evident efficacy, i.v.thrombolysis has a surprisingly low successful recanalization rate, which ranges between 20% and 30%, depending on the site and on the extension of arterial occlusion. To enhance the effect of i.v.thrombolysis and speed up clot lysis, the use of ultrasound (US) has been evaluated in several studies.

In most stroke units the access to ultrasound for the diagnosis of intracranial arterial occlusion is quite simple, due to the wide availability of transcranial Doppler among the clinical tools of vascular neurologists. A Transcranial Doppler (TCD) and/or a Transcranial color-coded Doppler (TCCD) are usually performed in the acute phase of IS, to detect and localize the arterial occlusion causing it and to monitor the recanalization following tPA infusion. Recently, experimental and clinical studies have consistently demonstrated the ability of US to enhance enzymatic thrombolysis. This type of treatment is called SonoThrombolysis (ST) [7, 8, 9, 10, 11, 12, 13].

Sonothrombolysis is usually performed in patients with a documented arterial occlusion by insonation of major intracranial vessels, mainly the middle cerebral artery. US increases the penetration of circulating tPA into the thrombus, promotes the breaking and cleaving of the fibrin polymers, and improves the binding affinity of tPA to fibrin. Thus, US accelerates enzymatic fibrinolysis through non-thermal mechanisms and through the motion of fluid in and around the thrombus. Moreover, recent experimental studies provided new insights in comprehension of ST mechanisms: the modulation of NO seems to help recanalization even for small vessel occlusions [14].

A meta analysis of randomized and non-randomized trials on ST [15] and a Cochrane Review of all the randomized studies published on ST [16] reported stimulating results: there were more recanalizations (Fig. 1), better clinical outcome (Fig. 2), with no effect on mortality (Fig. 3). An increase of asymptomatic and symptomatic hemorrhages was mainly due to the concomitant use of microbubbles (Fig. 4) [16, 17, 18, 19, 20], further enhancing clot lysis and blood brain barrier (BBB) disruption. Nevertheless, other studies reported no effect of US on BBB and did not show any increase of apoptosis and markers of tissue damage outside the infarcted area [21]. The possible usefulness of microbubbles is a promising field for researchers and for drugs development.

There are some ongoing trials, one no-profit Italian trial (ULTRAS), which has the goal to verify in a "real world" design the positive effect of ST on re-

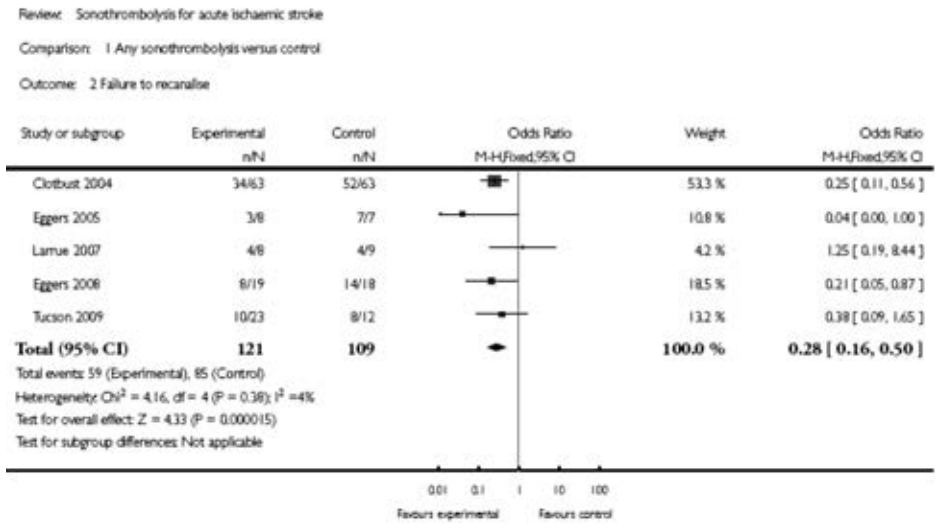

Fig. 1. **Analysis 1.2. Comparison 1 Any sonothrombolysis versus control, Outcome 2 Failure to recanalise.**

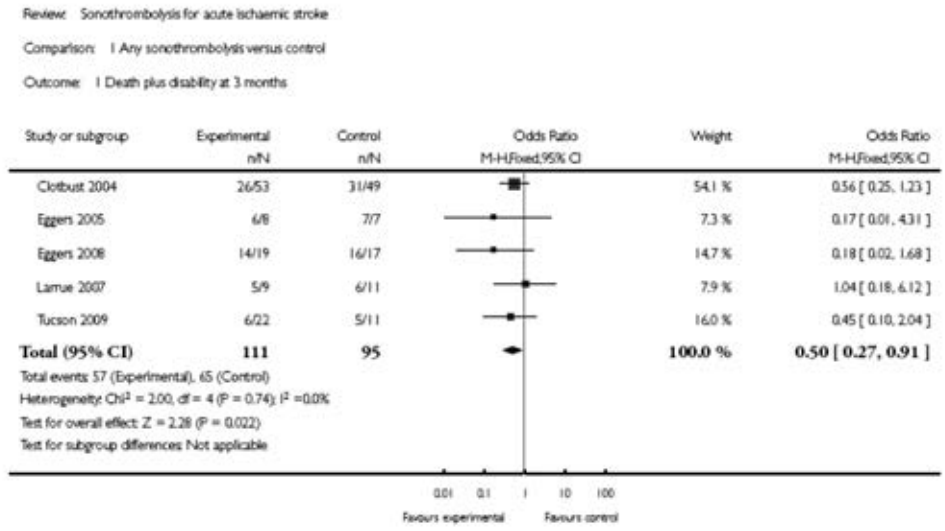

Fig. 2. **Analysis 1.1. Comparison 1 Any sonothrombolysis versus control, Outcome 1 Death plus disability at 3 months.**

canalization and on clinical outcome [22]. It is a multicenter, interventional, controlled, randomized study. Another ongoing trial is the "CLOTBUSTER", where an "Hand-free" helmet provides US administration, in a randomized design with a sham procedure, that has proven to be safe and applicable [23].

Both studies will provide new information of this promising, yet not completely proven, way of increasing tPA effect.

Waiting for the results of these two trial, ST represent a therapy still not-authorized for routine clinical use.

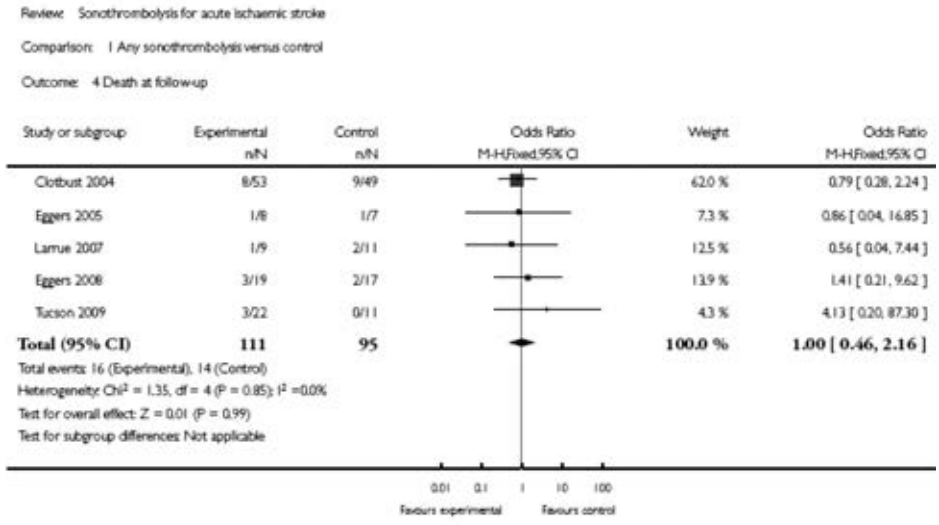

Fig. 3. **Analysis 1.4. Comparison 1 Any sonothrombolysis versus control, Outcome 4 Death at follow-up.**

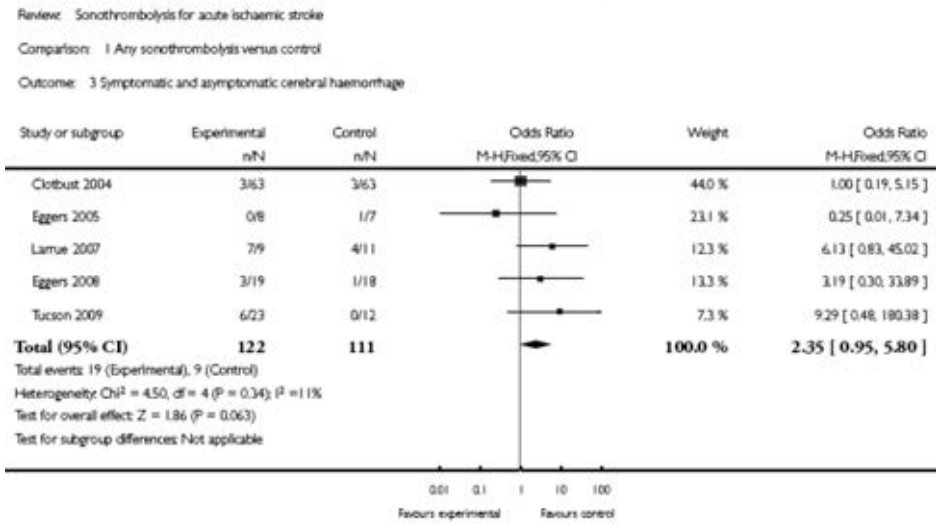

Fig. 4. **Analysis 1.3. Comparison 1 Any sonothrombolysis versus control, Outcome 3 Symptomatic and asymptomatic cerebral haemorrhage.**

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Ultrasound Imaging of Brain Parenchyma, Temporal Arteries and Orbita

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Key words:
brain parenchyma, diagnosis, orbita, temporal arteries, ultrasound imaging

Beside crucial role in the diagnosis of the morphological and hemodynamic changes of the cerebral vasculature, during last years, novel neurosonological methods (transcranial brain parenchyma sonography-TCS, temporal arteries ultrasonography, echosonography of the optic nerve and retrobulbar vessels) find their important place in the diagnosis of neurodegenerative and psychiatric diseases, temporal arteritis, as well as optic nerve and ocular vessels changes.

TCS is a highly sensitive non-invasive ultrasound method for detection of early and highly specific echogenic changes in basal ganglia of patients suffering from some neurodegenerative diseases such as Parkinson's-, Huntington's- and Wilson's disease, secondary parkinsonian syndromes, spinocerebellar ataxias, some forms of dystonia. Changes of the brainstem raphe echogenicity have been shown to be highly prevalent in patients with unipolar- as well depression associated with certain neurodegenerative diseases. That why TCS is valuable neuroimaging method for early and differential diagnosis and follow-up of patients with neurodegenerative and psychiatric diseases.

Ultrasonography of the temporal arteries revealed in 70-90% of patients with a clinical suspicion of temporal arteritis, specific sonographic changes: a) circumferent hypoechogenic wall thickening-halo, b) segmental stenosis or occlusion of temporal arteries and c) lack of temporal arteries compressibility.

Noninvasive echosonography of the optic nerves could easily reveal changes of the intracranial pressure (intracranial hypo- or hypertension) while duplex sonography could easily detect central retinal artery or vein occulsion.

Transcranial brain parenchyma sonography

Transcranial sonography (TCS) is a relatively new ultrasound diagnostic method which displays echogenicity of the brain tissue through the intact skull.

Besides the specific substantia nigra (SN) hyperechogenicity in about 90% of Parkinson's disease (PD) patents, that was first time described in 1995 by Becker et al. [1], numerous TCS studies reported other specific ultrasound features in various other neurodegenerative diseases.

Structural abnormality of the midbrain raphe displayed as reduced echogenicity or invisible brainstem raphe (BR) was found in patients with unipolar- and depression associated with some other neurological diseases [2, 3, 4, 5]. Modern TCS systems have a possibility to display deep brain structures with a very high lateral and axial resolution similar to that of magnetic resonance imaging (MRI) in clinical applications [6].

Based on the consensus guidelines it is suggested to perform TCS scanning through the temporal acoustic bone windows, as it is suggested for transcranial vascular ultrasound. Guidelines suggest using modern ultrasound equipped with 2.0- to 3.5-MHz phased-array transducers [7-9]. For the optimal insonation of brain structures, TCS parameters should be set as follows: dynamic range between 45 and 50 dB, insonation depth should be 14-16 cm; individualized adaptation of time gain compensation and brightness of the ultrasound image in order to achieve the best possible visualization. After clear ultrasound depiction of the basal ganglia structures it is suggested to fix and zoom ultrasound picture in order to provide optimal conditions for further ultrasound measurements. The scanning is performed at several axial levels through the brainstem and the thalami [7, 8, 9].

At the first scanning level, the butterfly shaped hypoechogenic brainstem surrounded by the highly hyperechogenic basal cisterns can be visualized. At this axial scanning level, the echogenicity of the ipsilateral SN, red nucleus (RN) and the BR could be evaluated (ig. 1) [7, 8, 9].

The best-validated method to measure and grade SN echogenicity is the planimetric measurement of SN echogenic area in axial plane. Hyperechogenic area is measured by encircling the outer circumference of the hyperechogenic area and is automatically displayed in square centimeters. According to consensus guidelines [7, 8] "a marked SN hyperechogenicity is considered, if the planimetrically measured echogenic area exceeds a cut-off value defined by the 90%

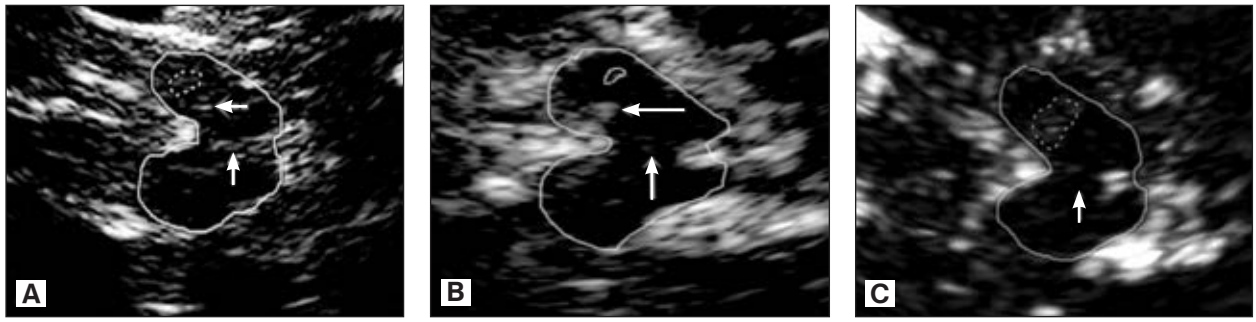

Fig. 1. *Axial TCS images (mesencephalic level). The butterfly-shaped midbrain was encircled for better visualization (full line). Thick arrow indicates BR; thin dotted arrow depicts RN; SN is encircled with dotted line.* ***(A)*** *Mesencephalic brainstem of a healthy individual with normal, nearly invisible SN and normal, highly echogenic BR which has the same echogenicity as the RN;* ***(B)*** *Mesencephalic brainstem of a patient with unipolar depression with normal, nearly invisible SN and abnormal, reduced echogenicity of the BR* ***(C)****; Mesencephalic brainstem of a PD patient with depression displays marked unilateral hyperechogenicity of the SN and abnormal, reduced echogenicity of the BR. Echogenic area of the right SN was encircled with dotted line for computerized measurement.*

percentile of measures in normal population, and moderate SN hyperechogenicity, if the measured area ranges in-between the 75% and 90% percentile of measures in healthy population". Planimetrically measured reference values of hyperechogenic SN areas range between 0.18 and 0.24 cm^2 depending on ultrasound systems applied.

IBR is normally depicted as highly echogenic continuous line which has similar echogenicity to that of the RN or surrounding cerebral white matter (Fig. 1) [9, 10].

Based on the TCS guidelines, BR echogenicity is rated semiquantitatively, preferable using a two-point grading system (grade 0: invisible, hypoechogenic or interrupted BR representing pathological finding; grade 1: highly echogenic continuous BR, as a normal finding) are suggested [7, 9, 10]. Due to variations in transparency of temporal bone windows it is suggested to scan BR always from both sides. If the BR can be depicted as continuous hyperechogenic line from at least one side, then it is rated as a normal (Fig. 1) [9, 10].

To display the thalamic axial plane level the ultrasound probe should be tilted 10-20 degrees upward. Very important landmark of the thalamic or ventricular level is the usually highly echogenic pineal gland (Fig. 2) [7, 8, 9].

The thalami are normally depicted as iso/hypoechogenic round structures next to the third ventricle. Hypoechogenic structures of thalami and ventricles help to differentiate the anatomical site of caudate nucleus (CN) and lenticular nucleus (LN) [7, 8, 9 , 10].

At the same level, the transverse diameters of the third ventricle which is depicted between the two hyperechogenic lines representing ependyma, as well as diameter of contra lateral frontal horn of the lateral ventricle can be measured (Fig. 2) [8, 9].

Normal TCS values for the ventricular system diameters depend on age, but it could be roughly accepted that normal diameter of the third ventricle is up to 10mm, and for the frontal horns of lateral ventricle up to 20 mm [7, 8, 9].

Echogenicity of contralateral thalamus, contralateral LN and contralateral CN should be evaluated semi-quantitatively at this level.

In normal conditions, these BG have the same echogenicity as surrounding brain parenchyma (Fig. 2), they are isoechogenic. Any hyperechogenic area at the anatomical sites of CN and/or

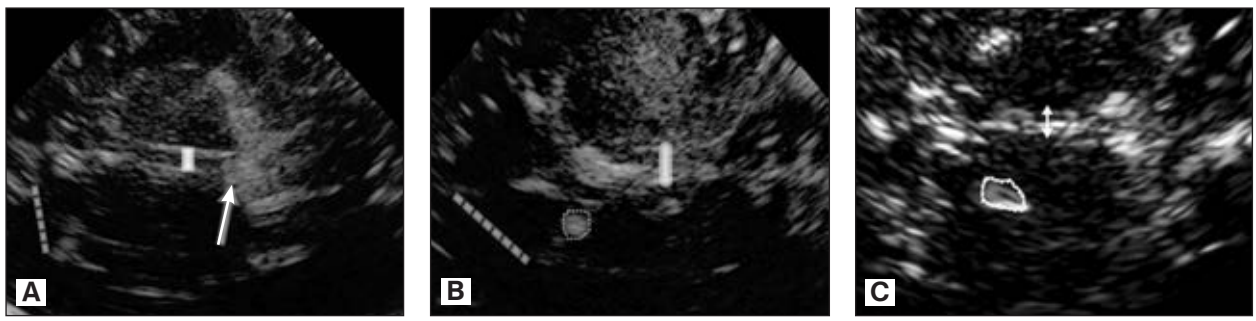

Fig. 2. *Sonographic images at the level of thalami (ventricular system).* ***(A)*** *Normal finding at the thalamic level, BG and thalami are invisible i.e. isoechogenic with surrounding cerebral white matter; normal diameters of the third ventricle (full line) and the frontal horn of the lateral ventricle (dotted line); full thick arrow depicts hyperechogenic pineal gland.* ***(B)****; Hyperechogenicity of the CN (encircled with dotted line), located next to the frontal horn of the lateral ventricle (depicted with the dotted line, normal diameter);* ***(C)*** *Hyperechogenicity of the LN (encircled with dotted line) located close to the third ventricle (depicted with arrow, normal diameter).*

LN is pathological. In that case, hyperechogenic signals could be measured planimetrically as it was described for SN (Fig. 2) [7, 8, 9, 10].

TCS in PD and atypical parkinsonian syndromes (APS)

SN hyperechogenicity above the cut-off values as a typical finding in PD patients (Fig. 1) was the first time described by Becker two decades ago [1]. SN hyperechogenicity could be found unilaterally or asymmetrically bilaterally. This finding has been also showed by many other research groups in the last decades [11, 12].

SN hyperechogenicity has also been detected in 8-10% of healthy people [13]. Healthy subjects with SN hyperechogenicity may show functional deficits in the nigrostriatal dopaminergic pathways, with "soft motor signs and symptoms" occurrence. SN hyperechogenicity on TCS in healthy individuals has been shown to reveal up to 20-fold increased risk of developing PD during up to five years follow-up period [13].

The reasons for SN hyperechogenicity in PD are not elucidated yet. It is possible that SN hyperechogenicity reflects pathological alterations related to an increased SN iron and possible other trace metals content [1, 12, 13], and may represent a susceptibility marker of nigrostriatal dopaminergic system vulnerability.

Typical finding of SN hyperechogenicity in patients with idiopathic PD is not frequent in atypical parkinsonian syndromes (APS) (multiple system atrophy-MSA and progressive supranuclear palsy-PSP), or vascular-Parkinsonism (VP).

TCS studies showed that "SN hyperechogenicity discriminates PD from APS (MSA and PSP) with a sensitivity of 92% and a specificity of 80%" [14]. On the other side, basal ganglia hyperechogenicities (primarily LN) could be specifically seen in APS but very rare in PD [14, 15]. The finding of BG hyperechogenicity with normal echogenicity of SN could be very helpful in discriminating PD from APS. An increase in the diameter of the third ventricle (>10mm) usually without SN hyperechogenicity but occasionally with LN hyperechogenicity, has been described in PSP but not frequently in PD patients [14, 15].

It is even possible to differentiate, based on TCS in addition to clinical characteristics, two different clinical forms of PSP: "classical" form known as Richardson's syndrome (PSP-RS) and another form known as PSP-Parkinsonism (PSP-P) [16]. In the recent study, our group showed that subgroup of patients with PSP-RS have significantly higher prevalence of LN hyperechogencity and significant dilatation of the third ventricle, while patients with PSP-P had significantly higher prevalence of pathological SN hyperechogenicity (73 vs. 14%), with significantly larger maximal area of SN hyperechogenicity [16].

TCS could be also an important additional diagnostic tool to differentiate between PD and VP. Namely, patients with VP in majority of cases do not have pathological hyperechogenic signals of SN and other basal ganglia structures. VP patients usually express pathological findings on vascular examination, showing increased blood flow velocities and/or pulsatility indexes as typical markers of intracranial vessels atherosclerotic changes as a background for VP [15].

EFNS/MDS-ES recommended application of TCS with the highest level of recommendation for the diagnosis of PD, the differential diagnosis with secondary and atypical Parkinsonism, and the detection of subjects at risk for PD [17].

As the TCS examination is highly operator dependent, this recommendation is valid only for adequately trained and very experienced sonographers.

TCS in other neurodegenerative diseases with movement disorders

TCS found its place as the diagnostic tool in several other neurodegenerative diseases characterized with movement disorders.

Two independent TCS studies showed specific echogenic changes of basal ganglia in patients with Wilson's disease (WD). Walter et al. [5] investigated 21 consecutive WD patients (18 with neurological form of the disease), and found increased LN echogenicity on at least one side in all assessed neurologically symptomatic and in 2 of the 3 patients with hepatic form of WD. Proposed explanation for LN hyperechogenicity in patients with either neurologic or hepatic form of WD, was increased copper content. SN hyperechogenicity was found in almost half of WD patients in the same study (10 out of 21) without ventricular system dilatation. Observed TCS changes were also present in some of patients with normal brain MRI [5].

We published results in larger group of "54 consecutive, clinically stable patients with WD who were classified as predominantly neurologic or hepatic form of the disease and were adequately assessable by TCS from both sides. TCS showed significantly higher prevalence of SN and LN hyperechogenicity in WD patients in comparison with healthy controls. Moderate to marked SN hyperechogenicity was found in 31.5% of our WD patients (42% and of those with predominantly neurologic form and 7% with hepatic form of WD). SN hyperechogenicity was also found in 8% of healthy controls in our study. Disease severity correlated with the hyperechogenicity of SN and with the width of the third ventricle that was significantly higher in patients with neurologic form of WD" [18].

Results of both TCS studies in WD patients, confirmed the ability of the method for early detection of trace metals in the basal ganglia (probably copper and possibly iron and manganese).

Similar findings were observed in some other neurodegenerative diseases with trace metals accumulation. Our group conducted MRI parallel to TCS in 5 unrelated patients with pantothenate kinase-associated neurodegeneration (PKAN), caused by PANK2 mutations [19]. "All patients in our study had an eye of the tiger sign on MRI. Hypointense lesions on the T2-weighted MRI images were restricted to the globus pallidus (GP) and SN. TCS also revealed bilateral hyperechogenic areas restricted to the LN and SN, with normal values of the third ventricle diameter. Both TCS and MRI findings in PKAN patients are in accordance with the pathological findings that accumulation of iron, even in advanced cases, is restricted to the GP and SN, suggesting selective involvement of these brain structures" [19].

In patients with cervical and upper limb dystonia, TCS displayed hyperechogenicity of LN (in up to 80% of cases) which is usually more prominent contra lateral to the clinically affected side. LN hyperechogenicity is probably caused by increased copper and manganese content [4].

Two TCS studies revealed comparable frequencies of BG hyperechogenic changes as well as a similar pattern of basal ganglia lesions in spinocerebellar ataxia (SCA) type 2 and SCA type 3 [20, 21]. SN hyperechogenicity was a frequent finding in both studies (66.7% of those with SCA 2 and 73.3% with SCA 3), indicating a vulnerability of nigrostriatal dopaminergic system in these SCA patients. SCA 2 patients also showed significant dilatation of the ventricular system represented by increased diameters of the third ventricle on TCS [20, 21]. Although evidence of TCS alterations in ataxia is limited, with the proposed specific cerebellar examination plane the enlargement of the fourth ventricle and nucleus dentatus hyperechogenicity could be visualized as a characteristic finding in SCA3 as well as in SCA17 patients. Hyperechogenicities of pallidostriatal regions, especially if marked and/or bilateral could be very useful and specific sonographic feature to differentiate between movement disorders with dominant extrapyramidal or ataxic clinical features [20, 21].

TCS in psychiatric diseases

Evidence from clinical, neuroimaging, biochemical and animal studies implicates basal limbic system and BR system involvement in the pathogenesis of the mood disorders, particularly depression. This is supported by typical TCS finding of low echogenicity or interrupted BR which is normally depicted as highly echogenic continuous line. Raphe hypoechogenicity or lack of visualization on TCS is observed in 50–70% of patients with unipolar depression and could be associated with responsiveness to inhibitors of serotonin-reuptake [10, 22]. These findings support a hypothesis that BR hypoechogencity that is frequently found in depressive disorders could be a marker of impaired central serotonergic transmission.

BR hypoechogenicity or interruption is even more frequent in patients with depression associated with suicidal ideation. It was shown that even 86% of these patients had TCS abnormalities of the BR. This was highly significant when compared with the same variable frequency (47%) of patients with major depression without suicidal ideation [22].

TCS revealed normal or even increased echogenicity (hyperechogenicity) of BR in bipolar disorder, without SN or other basal ganglia echogenicity changes. It was associated with significant ventricular system dilatation (the third ventricle), irrespective of the existing disease conditions or stages [22].

Characteristic PD finding of SN hyperechogenicity, was also frequently found in patients with depression. Those patients who had depression were found to have strong relationship between motor asymmetry and reduced verbal fluency and observed SN hyperechogenicity. This relationship was even stronger in younger patients (< 50 years) and independent from age in those who had reduced echogenicity, invisible or interrupted BR (32). Increased frequencies of PD-like TCS findings in patients with depression require them to be screened for sonographic and clinical signs of early, premotor PD [2, 3, 22].

One TCS study also showed that "the echogenicity of SN was significantly larger in children with attention deficit hyperactivity disorder (ADHD) in comparison with healthy controls (F1.42= 9.298, p=0.004, specificity was 0.73 and sensitivity 0.82), without influence of age or sex" [23]. SN hyperechogenicity in ADHD patients might be explained by a developmental delay followed by structural changes of basal ganglia structures. This assumption was confirmed by recent neuroimaging studies that have showed structural alterations in the basal ganglia of patients with ADHD [23].

Ultrasonography of temporal arteries

Temporal arteritis (TA), also known as giant cell or gigantocellular arteritis, is a chronic vasculitis of medium and large-sized blood vessels, in particular the main cervical branches of the aorta, with particular affinity to the temporal arteries and eye-supplying arteries. The most difficult compli-

cation of TA is visual loss, however in rare cases stroke can occur (3–8 %) with the predominance for vertebrobasilar circulation [24].

For differentiating TA from other forms of vasculitis, the American College of Rheumatology (ACR) formulated five classification criteria for TA: a) age over 50 years at onset, b) headache of new onset, c) scalp tenderness or decreased pulse of the temporal artery, d) erythrocyte sedimentation rate (ESR) > 50 mm/h and e) positive temporal artery biopsy revealing a necrotizing arteritis. The presence of three of these five criteria is associated with 93,5% sensitivity and 91,2% specificity for the diagnosis of TA [25]. Other serologic markers beside ESR such as C-reactive protein, platelet count, interleukin-6 and fibrinogen can provide additional information in favor of the TA diagnosis [24].

Temporal artery biopsy is still a gold standard for diagnosis, however in recent years color duplex ultrasound examination has been proposed as a useful diagnostic screening tool in cases of TA suspicion. Schmidt et al. [26] first described the edematous wall swelling of the temporal arteries, characterized sonographically as a hypoechoic or anechoic circumferential mural thickening localized around the arterial lumen, with a diameter ranging from 0.3–2.0 mm (Fig. 3). This finding was named as the "halo sign". Two other parameters considered relevant for the diagnosis of TA were described: stenosis and occlusion. Stenosis, characterized by a narrowing of the lumen, was defined as a segmental increase in blood flow velocity two times greater than in the region before the stenosis. Acute occlusion is revealed by the absence of color signal in a segment of temporal artery [26].

The sensitivity of ultrasound was highest when all three findings (halo, stenosis and occlusion) were present. The sensitivity of halo alone was lower, but the specificity was high. The weighted sensitivity and specificity of the halo sign were 69% (95% CI, 57% to 79%) and 82% (CI, 75% to 87%), respectively, compared with biopsy and 55% (CI, 36% to 73%) and 94% (CI, 82% to 98%), respectively, compared with ACR criteria. Stenosis or occlusion was an almost equally sensitive marker compared with either biopsy (sensitivity 68%) or ACR criteria (sensitivity 66%) [27].

For correct diagnosis, the appropriate examination technique and the experience of the sonographer are very important. There is a need for high quality color duplex ultrasound equipment, with standardized adjustments and a high frequency (> 8MHz) linear transducer [26]. False positive and negative halos may be seen in ultrasound examination. It is important to take care about the color gain during insonation, while if it is inappropriate could give false positive or negative results. Ultrasound is not able to differentiate between TA and other vasculitis that can involve the temporal arteries.

The consistently higher specificity serves to substantially increase suspicion when a halo sign is present. Recently published novel vascular ultrasound phenotype – namely visibility vs. loss of visibility of the TA upon transducer-imposed artery compression (compression sign that is absent in the diseased artery, i.e. upon transducer compression of the temporal artery it remains visible) could in combination with halo sign significantly increase the sensitivity and the specificity of sonography for the TA diagnosis [28].

The greatest utility of ultrasonography may be in cases with bilateral-halo signs. If high specificity in these cases is indeed confirmed with further investigation, the necessity of a temporal-artery biopsy in such cases may be questionable. Another role that has been suggested for ultrasound is direction of the temporal artery biopsy so as to avoid skip lesions. Finally, ultrasound of proximal upper extremity arteries had been shown to aid in the diagnosis of the large vessel variant of giant-cell arteritis (in which the aorta and its branches are primarily involved) [24, 25, 26].

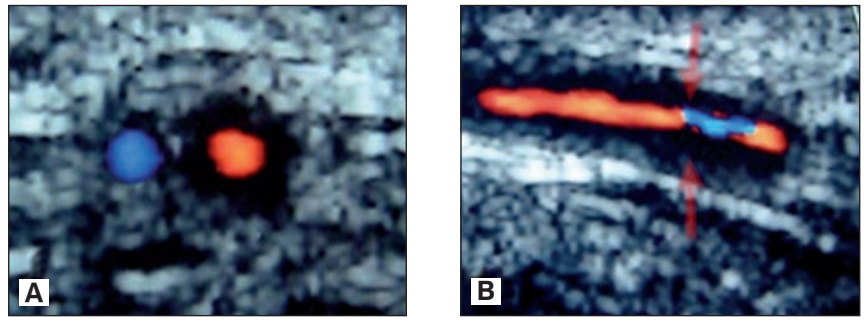

Fig. 3. *Duplex scan of the left superficial temporal artery of a 80-year-old woman with positive temporal artery biopsy, showing in cross-* ***(A)*** *and longitudinal-* ***(B)*** *sections circumferential hypoechogenic edematous arterial wall thickening ("halo sign") depicted with red arrows in the longitudinal section.*

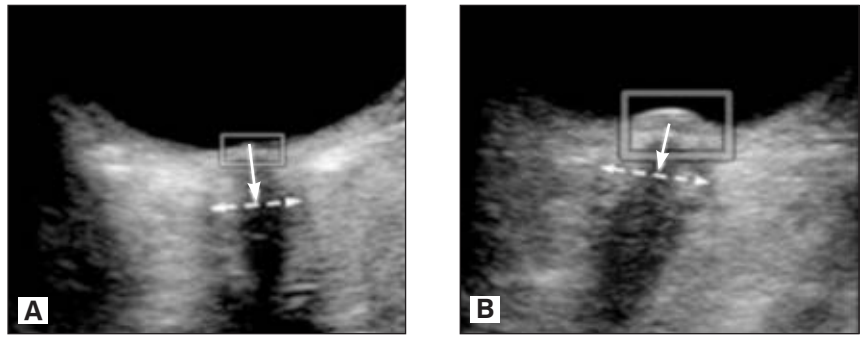

Fig. 4. *Axial orbital B-mode scan with longitudinal depiction of the optic nerve behind the optic bulb (optic nerve head) with measurement of ONSD.* ***(A)*** *Normal ONSD in healthy person (dotted arrow) is measured 3 mm behind the optic nerve head (depicted in rectangle).* ***(B)*** *Increased ONSD (dotted arrow) and optic nerve head edema (in rectangle) caused by increased intracranial pressure.*

Ultrasound imaging of orbita

For the insonation of the orbital and retroorbital structures we use linear transducers 8-15MHz with the acoustic power settings based on the ALARA principle (''as low as reasonably achievable'') to avoid possible damage of the ocular lens and retina.

Retrobulbar segment of the optic nerve could be visualized in axial scanning plane while optic disc and nerve are depicted longitudinally. It is recommended to depict the nasal side on the left side of the ultrasound B-mode image (Fig. 4A) [29].

Conventionally, optic nerve sheath diameter (ONSD) which is an extension of intracranial subarachnoidal sheaths is measured 3mm behind the optic nerve head (Fig. 4A), and is calculated as a distance between outer hyperechogenic areas that surround optic nerve [29].

As part of the central nervous system the optic nerve is surrounded by cerebrospinal fluid and by meninges, and any changes of the intracranial pressure have an influence on ONSD. Geeraerts et al. suggested normal average values for the ONSD of 5.1 ± 0.5 mm. ONSD values between 5.7 and 5.9 mm represent risk marker for increased intracranial pressure (ICP) particularly in patients with intracranial bleeding or head trauma (Fig. 4B) [29].

Transbulbar sonography with measurement of ONSD has a sensitivity of 90% and specificity of 85% to predict increase of ICP.

On the contrary, decreased ONSD bellow 4.7 mm could be found in patients with intracranial hypotension, either idiopathic or iatrogenic [30].

Differentiation between arteritic or embolic central retinal artery (CRA) occlusion is a diagnostic challenge specially in older patients with ischemic optic neuropathy (ION). Presence of the so called ''spot sign'' (hyperechogenic embolic material) in the optic nerve head at the projection of CRA, with very high probability points toward embolic occlusion of the CRA (Fig. 5). On the contrary, vasculitic hypoperfusion in temporal or arteritis of other etiology is associated with decreased or absent flow in the CRA and lack of ''spot sign'' [31]. This etiological differentiation which easily could be obtained with ocular sonography has important therapeutic implications. Sensitivity for detection of the embolic CRA occlusion based on the presence of ''spot sign'' is 83% (95% CI: 65-99%), and specificity for exclusion of the vasculitic causes of ION is 100% (95% CI: 65-100%) [31].

Conclusion

TCS is valuable, reliable and very useful neuroimaging method that has an important place in the early and differential diagnosis of psychiatric and neurodegenerative diseases. Sonography is also an important additional non-invasive diagnostic method for patients with clinical suspicion for TA that could be also used to guide temporal artery biopsy and to follow-up therapeutic success. Ultrasonography of the optic nerve and retro bulbar

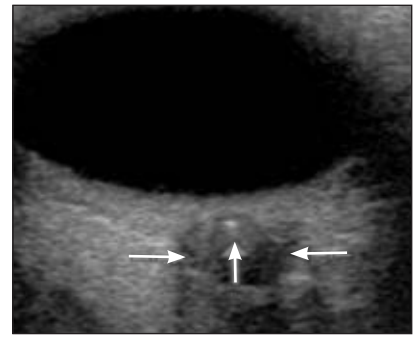

Fig. 5. *B-mode orbital sonography with longitudinal depiction of the optic nerve (dotted blue arrows) and hyperechogenic ''spot sign'' in the optic nerve head (red arrow) which represents embolic material that occluded the distal segment of the right CRA in patient with sudden unilateral visual loss.*

vessels is novel method to identify and follow-up patients with ICP changes as well as to differentiate between vasculitic or thromboembolic causes of sudden visual loss (ION).

All mentioned ultrasound methods are easily applicable, non-invasive, cost effective, bedside and could be repeated as much as needed.

Certain limitations are associated with non-transparent acoustic bone windows for TCS in small minority of patients and with the operator-dependence for all described modern ultrasound methods.

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Cerebral Vasomotor Reactivity in Clinical Settings

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Key words:
carotid stenosis, cerebral vasomotor reactivity, transcranial Doppler sonography

The cerebral vasomotor reactivity (VMR) indicates the ability of the cerebral arterioles to change their vascular tone under external stimuli. Greatest influence on the VMR exert age, endothelial functions and blood rheological properties. The most frequent influences are inhalatory induced changes in the partial pressure of carbon dioxide and infusion of acetazolamide. The alterations in the cerebral circulation are examined mainly with transcranial Doppler sonography or magnetic resonance imaging. In patients with carotid stenoses and cerebral infarctions and also in other diseases the estimation of the VMR is important for evaluating the pathogenetic mechanisms and the clinical outcome and for selecting the therapeutic behavior in these patients.

The cerebral vasomotor reactivity (VMR) indicates the ability of the cerebral arterioles to change their vascular tone under external stimuli. The hemodynamic response after applying stimuli for assessment of the VMR is mainly related to metabolic mechanisms. The integrity of the vascular endothelium [22] and the influence of some endothelial factors, especially of NO are important for the regulation of the VMR. The tone of the cerebral arterioles is particularly sensitive to changes in the carbon dioxide partial pressure ($PaCO_2$). However under the CO_2 influence the diameter of the basal cerebral arteries remains almost unchanged [1, 11].

The effect of different factors on the VMR like chronic hyperglycemia or high values of plasma viscosity or estrogens are established [32]. The cerebral vascular reactivity reveals diurnal fluctuations with morning reduction. It is also influenced by exercise training [14], high altitude [20] and especially by the age factor. Ageing causes reduction of the cerebral VMR to CO_2 and this reduction is associated with impairment of the cerebral autoregulation, increased vascular stiffness [6], slow gait speed and frequent falls [27]. Also sex dependence with significantly higher VMR in women than men was found. The VMR assessment shows greater absolute measures in the anterior than the posterior circulation [26]. In orthostatic stress attenuated VMR could be observed and in this case it reflects the reduces cerebral vascular reserve to compensate the instability of the systemic circulation [13].

When measuring the cerebrovascular reactivity the most frequently used vasoactive provocation is 5-7% CO_2 inhalation. Monitoring of the mean blood flow velocity in the middle cerebral artery (MCA) by transcranial doppler sonography (TCD) and of $PaCO_2$ is performed and the VMR is calculated as the ratio of the percent increase of blood flow velocity due to the induced hypercapnia towards its values at normocapnia and the absolute increase of p CO_2 at the same conditions[28]. The method is based on the conception that when the cerebral arterioles are maximally dilated during impaired cerebral autoregulation, the further vasodilation after provoked hypercapnia would be strongly restricted. Recently new techniques of the test with rebreathing and control of the ispired CO_2 and combining this with an instrument for control of the lung gas exchange region[5]. Recent studies have shown good reproducibility and reliability, especially when performing the test in sitting than lying posture [22]. The cerebral VMR can be also estimated with acetazolamide infusion [1, 5].

The test with breath-holding for 30 sec, where the induced hypercapnia causes vasodilatation is easy to perform and suitable for screening. The test could be expanded with applying of hyperventilation (hypocapnia) and consequent calculation of the index of total vasomotor reactivity and the vasomotor range. The hypocapnia exerts vasoconstrictive effect and it has been used for mapping of the cerebral VMR. Sometimes its application could induce heterogenic reaction, especially in traumatic brain injury. The disadvantage of the breath-holding test is the inability to control the lung ventilation [5].

In addition to TCD the cerebral VMR is assessed with other methods for evaluation of the cerebral blood flow and the cerebral blood volume when applying the same stimuli: xenon-computerized tomography (Xe/CT), perfusion or phase-contrast positron emission tomography

(PET), single photon emission comuterized tomography (SPECT). These investigations are more expensive, they are associated with radiation and often reveal variable results. During the last years different magnetic-resonance imaging (MRI) techniques for examination of the cerebral VMR: blood oxygen level dependent MRI (BOLD – MRI) with estimation of the cerebral oxygenation, arterial spin labeling MRI (ASL – MRI) with estimation of the arterial blood flow [19] and quantitative MRI angiography [3] have been used. BOLD – MPI gives possibility for cerebral VMR mapping and for evaluation of its regional heterogeneity. Comparative studies have shown good correlations between the results of the MRI and TCD tests when examining the cerebral VMR in one and the same patient. When comparing the parallel investigation of the VMR with PET and TCD however, coincidence of the results in only half of the patients with symptomatic occlusions of the internal carotid arteries was found [24].

The basic clinical application of the tests for estimation of the cerebral VMR is in carotid pathology – stenoses or thromboses of the internal carotid arteries. Meta-analyses of prospective studies in a great number of patients with asymptomatic or symptomatic high-grade carotid stenosis or occlusion and decreased VMR have shown significantly increased risk of stroke or transient ischemic attacks [12, 17, 21]. The impaired VMR is associated with risk of mortality, cardiovascular or noncardiovascular, regardless of the presence or absence of stroke. In these cases the VMR is discussed to reflect the existence of systemic vascular damage [25]. A prospective study with evaluation of the VMR on admission and after 6 months in patients with acute stroke and symptomatic intracranial or extracranial stenosis shows better VMR values from the ipsilateral hemisphere in the patients with extracranial than with intractranial stenosis. The VMR measures from admission correlated positively with the Barthel index on the 6th month [29]. The impairment of the hemodynamic reserve capacity is frequently observed in patients with multiple asymptomatic subcortical infarctions, the results suggesting vasculopathy of the small vessels and hypoperfusion pathogenetic mechanism of their origin. When investigating patients with cerebral infarctions and symptomatic carotid stenoses Jolnic W. et al. [15] established that the TCD examined VMR has not identified the subgroup with high risk of stroke recurrence. Our studies with estimation of the VMR in the MCA in patients with unilateral cerebral infarctions showed its bilateral decrease [30]. In cases with cerebral infarctions ipsilateral to high-grade stenosis or thrombosis of the internal carotid artery significant asymmetry of the VMR indices is observed with their decrease on the side of the vascular pathology.

It is found that the measurement of the VMR could be used for evaluation of the therapeutic interventions in patients with carotid disease. Improvement of the investigated with BOLD –MRI impaired VMR in patients with high-grade stenoses after carotid endarterectomy is reported [10]. In similar patients the subgroup with reduced VMR in the MCA is the only independent risk factor for new ischemic accident after carotid stenting [18].

A study in patients with subarachnoid hemorrhage shows that the abnormal VMR after CO_2 inhalation precedes the development of symptomatic vasospasm in the patients [2]. Our investigation in patients who underwent surgery for cerebral aneurisms revealed significant decrease of the total vasomotor capacity of the middle cerebral artery after the ventilation stimulus. Similar decrease in patients with type2 diabetes mellitus with expressed hyperglycemia and possible arteriolopathy was observed [7, 31].

Experimental and clinical studies reveal impaired VMR to hyper- or hypocapnia in patients with cognitive deficit and degenerative or vascular dementia. The reduced VMR in the both types of dementia prompts impairment of the cerebral microcirculation and helps for the choice of specific therapy [4, 16, 33]. Changes of the VMR have been also observed in patients with glaucoma, depression, epilepsy and others.

It was established that the impaired cerebral vascular reactivity was influenced by statin treatment [8, 9]. The effects of the statins are due to their influence on the smooth of the endothelial functions.

The evaluation of the VMR by measurement of the vasomotor capacity of the cerebral arteries and the effectiveness of the collateral circulation in patients with carotid pathology and cerebral infarctions and also in other diseases is important for the estimation of their pathogenetic mechanisms, choosing the therapeutic behavior and estimating the disease outcome in these patients.

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70-ГОДИШЕН ЮБИЛЕЙ 70TH ANNIVERSARY

Проф. Емилия Христова, дм

Prof. Emilia Christova, MD, PhD

Професор Емилия Христова оставя трайни следи в детското здравеопазване като доайен в българската неонатология. Тя е създател на първите неонатологични структури в България по европейски модел и на първия Медицински стандарт по неонатология.

Над 40 години от своя живот проф. Христова работи за модернизиране на детското здравеопазване и създаване на неонатологични екипи, способни да извършват първична ресусцитация в родилна зала, да спасяват високорискови новородени деца и да провеждат интензивно лечение. За подпомагане на тази дейност тя учредява Българската асоциация по неонатология и е неин първи председател. Тя е автор и съавтор на много научни трудове, учебници и ръководства по педиатрия и неонатология и се ползва с висок авторитет у нас и в чужбина.

Голямото човешко сърце на проф. Христова, опитът й в сферата на неправителствените организации и неизчерпващият й алтруизъм са генератори на националните благотворителни инициативи: "Силвия Вартан за България", "Българска Коледа", "Шанс за живот".

Българската асоциация по невросонография и мозъчна хемодинамика честити 70-годишния юбилей на своя учредител и заместник-председател проф. Емилия Христова, като й пожелава крепко здраве, дълъг и творчески живот!

ЧЕСТИТ ЮБИЛЕЙ!

Professor Emilia Christova leaves an everlasting track in child healthcare as a Doyen of Bulgarian Neonatology. She is the founder of the first neonatology structures in Bulgaria following an European model and the creator of the first Medical standard in Neonatology.

For more than 40 years now, professor Christova has been working to modernize child healthcare and to create neonatology medical teams, capable of performing primary resuscitation in the delivery room to save high-risk newborns and consequently to conduct intensive treatment. In order to develop and support this process of modernization, she established the Bulgarian Neonatology Association and was its first President. She is the author and co-author of many scientific papers, textbooks and manuals on Pediatrics and Neonatology. Her professional reputation is highly valued at home and abroad.

The great human heart of professor Christova, her experience with non-governmental organizations and last but not least – her endless altruism are the generators of a number of charities with a national cause like: "Sylvie Vartan for Bulgaria", "Bulgarian Christmas" and "Chance for Life".

Bulgarian Society of Neurosonology and Cerebral Hemodynamics congratulates the 70th anniversary of its founder and Vice-president Professor Emilia Christova and wishes her good health, long life and success in every initiative!

HAPPY JUBILEE!