UMF
IULIU HAȚIEGANU
UNIVERSITY OF
MEDICINE AND PHARMACY
CLUJ-NAPOCA
ROMANIA

# "IULIU HATIEGANU" UNIVERSITY OF MEDICINE AND PHARMACY DOCTORAL SCHOOL

# NEUROSCIENCE

## PROGRAM

2016-2017 | SECTION 1

MONDAY, 23 JANUARY AND FRIDAY, 27 JANUARY | UMF "IULIU HATIEGANU" | CLUJ-NAPOCA | ROMANIA

FRIDAY, 27 JANUARY AND SATURDAY, 28 JANUARY | RONEURO INSTITUTE | CLUJ-NAPOCA | ROMANIA

# PhD NEUROSCIENCE PROGRAM COORDINATOR

## Dafin F. Mureşanu

President of the Romanian Society of Neurology

Professor of Neurology, Chairman Department of Neurosciences
"Iuliu Hatieganu" University of Medicine and Pharmacy,
Cluj-Napoca, Romania

President of the Society for the Study of Neuroprotection and
Neuroplasticity (SSNN)

# INTERNATIONAL GUEST LECTURERS

## Tudor Jovin

Associate Professor of Neurology and Neurosurgery
at the University of Pittsburgh School of Medicine,
Director, UPMC Stroke Institute, USA

Director, UPMC Center for Neuroendovascular Therapy

President, Society of Vascular and Interventional
Neurology (SVIN)

## László Csiba

Chairman of the Department of Neurology
at the University of Debrecen, Hungary

President of Hungarian Neurological Society

Visiting Professor "Iuliu Hatieganu" University of
Medicine and Pharmacy, Cluj-Napoca, Romania

## Attila Csányi

Department of Neurology,
Petz Aladar County Hospital, Gyor, Hungary

## Milija Mijajlovic

Neurology Specialist, Neuroangiology Expert,
Assoc. Prof. of Neurology
Head of Neurosonology Unit

Neurology Clinic, Clinical Center of Serbia and
School of Medicine, University of Belgrade, Serbia

# PhD NEUROSCIENCE PROGRAM FACULTY 2016-2017

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Claudio Bassetti /Switzerland

Natan Bornstein /Israel

Michael Brainin /Austria

Michael Chopp /USA

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# COURSE PROGRAM

# COURSE PROGRAM

## JANUARY 23RD, 2017

"IULIU HATIEGANU" AUDITORIUM

23 GHEORGHE MARINESCU STREET | CLUJ -NAPOCA | ROMANIA

| | |
|---|---|
| 09:50 – 10:00 | Dafin F. Mureșanu /Romania<br>Welcome Address |
| 10:00 – 10:45 | Tudor Jovin /USA<br>Endovascular therapy for acute ischemic stroke:<br>The standard of care |
| 10:45 – 11:30 | Tudor Jovin /USA<br>Endovascular therapy for acute ischemic stroke. Future directions |
| 11:30 – 12:15 | Tudor Jovin /USA<br>The role of imaging in patient selection for acute stroke treatment with endovascular techniques |
| 12:15 – 14:00 | Session Break |
| 14:00 – 14:45 | Tudor Jovin /USA<br>Endovascular therapy for basilar artery occlusion |
| 14:45 – 15:30 | Tudor Jovin /USA<br>Management of extracranial carotid disease:<br>medical therapy, endarterectomy and stenting |

# COURSE PROGRAM

## JANUARY 27TH, 2017

"MULTIMEDIA" AUDITORIUM, "IULIU HATIEGANU"

UMF CLUJ-NAPOCA | 8 VICTOR BABES STREET | CLUJ -NAPOCA | ROMANIA

| | |
|---|---|
| 09:00 – 09:45 | László Csiba /Hungary<br>Bedside differential diagnosis on unconsciousness |
| 09:45 – 10:30 | László Csiba /Hungary<br>Unsolved questions of desobliteration therapy in acute stroke |
| 10:30 – 11:00 | Coffee Break |
| 11:00 – 11:45 | László Csiba /Hungary<br>Ancillary ultrasound techniques used in pharma trials |

## JANUARY 27TH, 2017

"RONEURO" INSTITUTE FOR NEUROLOGICAL RESEARCH AND DIAGNOSTIC

37 MIRCEA ELIADE STREET | CLUJ -NAPOCA | ROMANIA

HANDS ON SESSION

| | |
|---|---|
| 16:00 – 17:30 | Attila Csányi /Hungary<br>Intima-media thickness measurement as an objective non-invasive measurement tool of cardiovascular risk |
| 17:30 – 19:00 | Attila Csányi /Hungary<br>TCCD examination and its pitfalls |

# COURSE PROGRAM

## JANUARY 28TH, 2017

"RONEURO" INSTITUTE FOR NEUROLOGICAL RESEARCH AND DIAGNOSTIC

37 MIRCEA ELIADE STREET | CLUJ -NAPOCA | ROMANIA

HANDS ON SESSION

| | |
|---|---|
| 09:00 – 10:30 | Attila Csányi /Hungary<br>Optic nerve examination as the sign of elevated intracranial pressure |
| 10:30 – 12:00 | Attila Csányi /Hungary<br>Peripheral nerve/muscle neurosonology as a special technics supporting of EMG diagnosis and botulinumtoxin therapy |
| 12:00 – 12:30 | Coffee Break |
| 12:30 – 13:30 | Milija Mijajlovic /Serbia<br>Extracranial color Doppler examination (carotid and vertebral arteries, veins) |
| 13:30 – 14:30 | Milija Mijajlovic /Serbia<br>Transcranial brain parenchyma sonography |
| 14:30 – 15:30 | Lunch Break |
| 15:30 – 16:30 | Milija Mijajlovic /Serbia<br>TCD/TCCD ultrasound examination protocol |
| 16:30 – 17:30 | Milija Mijajlovic /Serbia<br>Temporal arteries, retrobulbar circulation, optic nerves |
| 17:30 – 18:30 | Milija Mijajlovic /Serbia<br>Cerebral microemboli detection, vasomotor reactivity, right-to-left shunt detection |

# INTERNATIONAL GUEST LECTURERS

# TUDOR JOVIN
USA

| | | | |
|---|---|---|---|
| Heinrich Heine Univ. of Dusseldorf, Germany | M.D. | 1990-1994 | Medicine |
| Intern, Pennsylvania Hospital Philadelphia, PA | | 1996-1997 | Internal Medicine |
| Resident , University of Pennsylvania , Pennsylvania Hospital, Philadelphia , PA | | 1997-2000 | Neurology Residency |
| Presbyterian University Hospital, Stroke Institute, Pittsburgh PA | | 2000-2002 | Cerebrovascular Fellow |
| Presbyterian University Hospital, Pittsburgh PA | | 7/2002-6/2004 | Fellow Interventional Vascular Neurology |

Dr. Jovin is the Director of the UPMC Stroke Institute, one of the highest volume vascular neuroscience centers in the country. He is an expert in interventional and non-interventional treatments of the entire spectrum of cerebrovascular disorders, including ischemic and hemorrhagic stroke.

He serves as principal investigator for the REVASCAT study, a randomized trial in Spain of endovascular therapy versus medical therapy for stroke due to large artery occlusion within 8 hours, as well as principal investigator for DAWN, a multicenter, international, randomized trial of endovascular therapy versus medical therapy in the beyond 6-hour time window. He has served or currently serves as a member of the executive/steering committee for several multicenter national and international trials, and serves as the site principal investigator/co-investigator for several local or multi-center clinical trials. He has published over 200 articles in peer-reviewed journals or book chapters.

As the former UPMC Stroke Fellowship Program Director and UPMC Neurointerventional Fellowship Program Director, positions he has held for over five years, Dr. Jovin has mentored numerous young neurologists or neurosurgeons who, in addition to acquiring the necessary clinical and procedural skills for successful clinical practice, have authored publications in leading peer-reviewed cerebrovascular disease journals.

Dr. Jovin is the immediate past President of the Society of Vascular and Interventional Neurology and serves on several other committees or boards of national and international societies (American Academy of Neurology, American Society of Neuroimaging,) and editorial boards of medical journals within his area of expertise (Stroke, Journal of Neuroimaging, Interventional Neurology). Dr Jovin's clinical and research activities are focused on the care of patients with cerebrovascular disorders.

# LÁSZLÓ CSIBA
## HUNGARY

Professor and chairman of the Department of Neurology at the University of Debrecen, Hungary since 1992.

- visiting scientist in the Max-Planck Institute for Neurological Research in Cologne (1981-83),
- one year in Kure City, Japan (1986)
- half year in Toulouse (INSERM, France).
- He is the founder of Hungarian Neurosonological Society,
- honorary member of Austrian Stroke Society,
- visiting professor of Belgrade, Cluj/Kolozsvár, Targu Mures/Marosvásárhely and Novi Sad/Újvidék University and Israel Association of Neurology.
- Editorial board member:"International Journal of Stroke", "Neurosonology (Japan)" "Clinical Neurosciences" and associate editor of "Frontiers in Stroke"
- Past president of the Hungarian Stroke Society, Chair of board of directors (Eur. Stroke Org.)
- Corresp. member of Deutsche Gesellschaft für Klinische Neurophysiologie und Funktionelle Bildgebung
- Between 2009 and 2013 he was the president of European Society of Neurosonology and Cerebral Hemodynamics.
- Since 2015 he is the president of Hungarian Neurological Society.
- Between 2005-2010, as chair of European Cooperation Committee of the European Federation of Neurological Societies he introduced the regional teaching course system of EFNS in middle and eastern European countries (neurosonology, acute stroke and prevention).
- He was awarded with the prize of European Stroke Conference, Eur. Neuroson. Soc. Cer. Hemodyn., Batthyány-Strattmann Prize (Ministry of Health), Francis Crick Award, Szentgyörgy (Ministry of Health) I and Lazarevics prize (Serbian Neurol Soc) for his activity in stroke care, education and research. The President of Hungarian Republic awarded him the Knight's Cross of Republic (for outstanding educational and clinical work).
- His department hosted two times the Stroke Summer Course of the European Stroke Organisation.
- During the last 11 years, his department performed more than 1300 iv. lysis on acute stroke patients and became an international clinical, educational and research center in the eastern part of Europe. stroke He published 246 papers (with IF::351,4 (independent citations of 3587 Hirsch-index:28) on stroke, neurosonology and stroke risk diseases.

# ATTILA CSÁNYI
## HUNGARY

PRESENT POSITION
Head of the Department, Aladár Petz Teaching Hospital (PAMOK), Dept. of. Neurology, H-9024 Győr, Vasvári Pál u. 2-4., Hungary
Associate Univ. Professor of Health Sciences at István Széchenyi University, H-9026 Győr, Egyetem tér 1., Hungary

EDUCATION
1981-1987: Ignác Semmelweis University, Budapest, Hungary, M.D. degree "summa cum laude"

PROFESSIONAL EXPERIENCE
1987-1991: Resident at the Department of Neurology, PAMOK
1992: special EEG course in OPNI, Budapest, Hungary
1992-1995: Consultant Neurologist at the Department of Neurology, PAMOK
1996-2001: Senior Consultant Neurologist Department of Neurology, PAMOK
1999-2003: Associate Professor of Health Sciences, István Széchenyi University
2002-present: Head of the Department of Neurology, PAMOK
2002: Ph.D. degree "summa cum laude"
2004-present: Associate Univ. Professor of Health Sciences, István Széchenyi University,
2014-2015: newly founded licence in neurosonology and vascular neurology

RESEARCH FELLOWSHIPS
1992: Vascular and experimental neurology fellowship at the Department and Institute of Neurology, University of Kuopio, Finland (Prof. Riekkinen, Prof. Sivenius, ass. Prof. Reinikainen).
1994-1995: Neurosonology fellowship at the Department of Neurology, Karl-Franzens University, Graz, Austria (Prof. Lechner, Prof. Niederkorn, ass. Prof. Horner)
1996: Epidemiology and carotid wall IMT measurement fellowship at the Department of Internal Medicine, Clinical Physiology and Epidemiology, Malmö, Sweden (Prof. Berglund)
1998-1999: visiting doctor at the Department of Neurosurgery, Chugoku Rosai Hospital, Kure City, Japan (Prof. Shima)

FIELDS OF INTEREST
Acute cerebral ischemia, ultrasonic carotid wall IMT measurement, transcranial Doppler and colour Doppler, quantitative EEG, autoimmune neurological disorders, movement disorders and botulinum toxin therapy

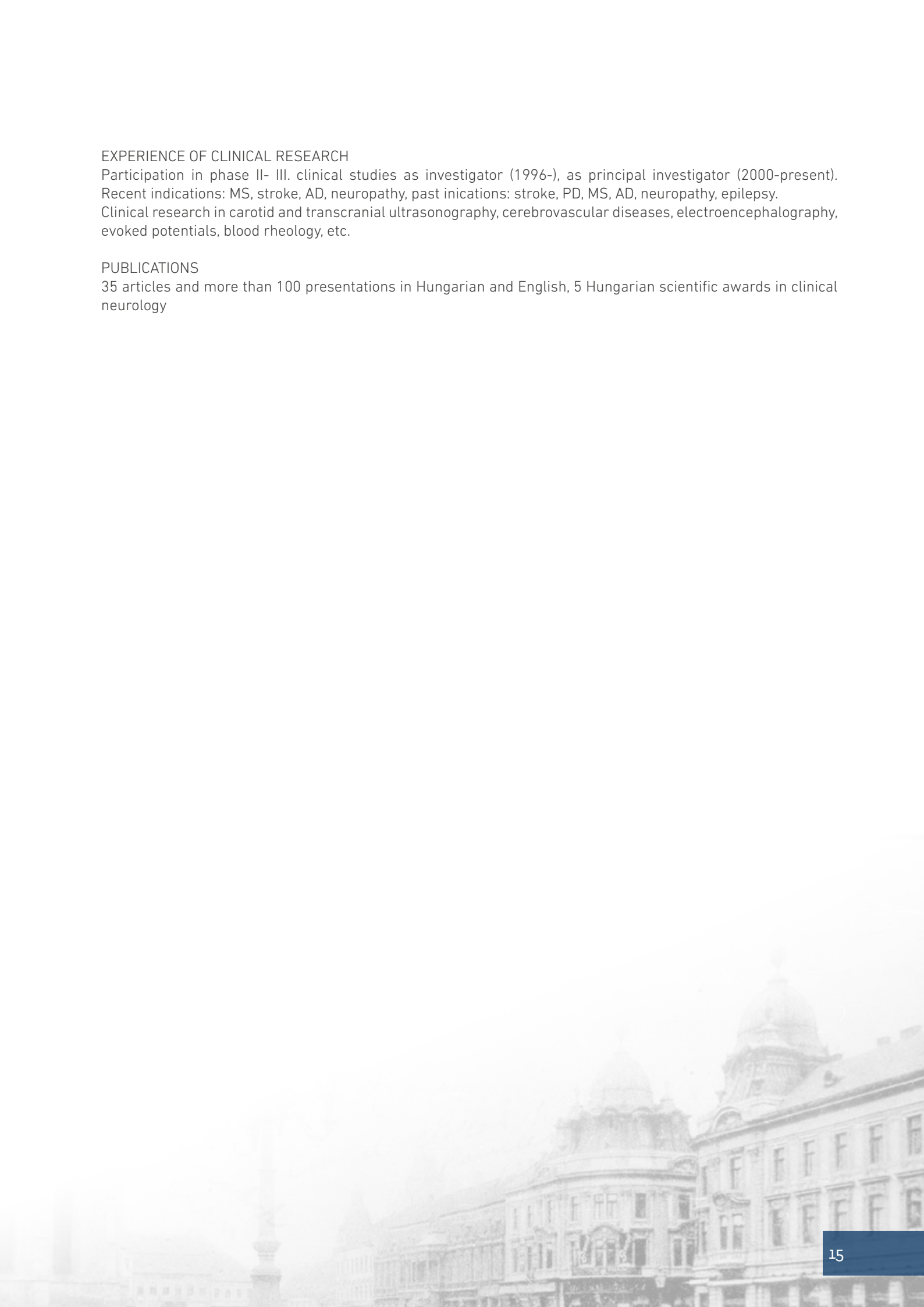
MEMBERSHIP
1993-present: Hungarian Stroke Association (leading member and vice-president)
1993-1997: Hungarian Neuroradiological Association
1994-1996: Section of Neurosonology, Hungarian Stroke Society
1995- Research Group of Neurosonology, World Federation of Neurology
1996-present: Hungarian Society of Neurosonology (secretary and president)
2004-present: Hungarian Society of Neurology and Psychiatry (leading member)
2004-2009: Hungarian Council of Neurology

EXPERIENCE OF CLINICAL RESEARCH

Participation in phase II- III. clinical studies as investigator (1996-), as principal investigator (2000-present). Recent indications: MS, stroke, AD, neuropathy, past inications: stroke, PD, MS, AD, neuropathy, epilepsy.
Clinical research in carotid and transcranial ultrasonography, cerebrovascular diseases, electroencephalography, evoked potentials, blood rheology, etc.

PUBLICATIONS

35 articles and more than 100 presentations in Hungarian and English, 5 Hungarian scientific awards in clinical neurology



# MILIJA MIJAJLOVIC
SERBIA

Education

| Year Attended | Date | Name & Location of Institution | Major |
|---|---|---|---|
| 1995 – 2001 Undergraduate studies | Graduated in July 2001. | School of Medicine, University of Belgrade | Doctor of Medicine (MD) |
| Student Tutor | 1998-2001. | Institute of path-physiology, School of Medicine, University of Belgrade | Path physiology of the central nervous system |
| Internship | 2001-2002. | School of Medicine, University of Belgrade | Neurology, Neuropsychology |
| General Practitioner License | July 2002. | Ministry of Health, Republic of Serbia | Board Certified MD (GP) |
| Postgraduate Master's degree studies in Neurology | 2001-2007. | School of Medicine University of Belgrade | Master's Degree (MSc) in Neurology<br>Thesis Title:<br>"The role of insulin resistance in ischemic brain disease" |
| Residence in Neurology | 2006-2009. | Institute of Neurology, Clinical Center of Serbia, Belgrade; School of Medicine University of Belgrade | Title: Board certified Neurologist |
| National expert in neuroangiology | 2005. - | National Society of Neuroangiology of Serbia and School of Medicine University of Belgrade | Title: Neuroangiologist |
| Scientific Researcher, Research Associate | 2009. - | Ministry of Sciences of Serbia; School of Medicine University of Belgrade | Scientific areas: Neurology, Neurosciences |
| Assistant Professor | 2012. - | School of Medicine University of Belgrade | Scientific Area: Neurology |
| Doctoral Studies | 2010-2015. | School of Medicine University of Belgrade | Title: PhD in Medicine (Neurology) |

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)

Member of the:

- Young Stroke Physicians Committee of the European Stroke Organisation (2015- )
- Teaching Course Sub-committee of the European Academy of Neurology (2016-)
- Executive Committee of the Neurosonology Research Group of the World Federation of Neurology (2013- )
- Scientific Committee of the European Society of Neurosonology and Cerebral Hemodynamics (2013- )
- European Academy of Neurology (EAN) Neurosonology Subspecialty Scientific Panel (2014- )
- Member of the Advisory Editorial Board of JUM (2014- )
- The Movement Disorders Society-MDS
- World Stroke Organization-WSO
- Board of the National Society of Neuroangiology of Serbia (2005- )
- Serbian Medical Society/Chamber
- President of the Scientific Committee of the Society of Young Serbian Neurologists (2012- )

# ABSTRACTS

## ENDOVASCULAR THERAPY FOR ACUTE ISCHEMIC STROKE: THE STANDARD OF CARE

TUDOR JOVIN
Associate Professor of Neurology and Neurosurgery at the University of Pittsburgh School of Medicine,
Director, UPMC Stroke Institute, USA
Director, UPMC Center for Neuroendovascular Therapy
President, Society of Vascular and Interventional Neurology (SVIN)

Acute ischemic stroke continues to be a major cause of permanent disability and death worldwide. Outcomes are particularly poor in patients presenting with large vessel occlusive disease with resultant ischemia and tissue injury in large and eloquent territories. Intravenous thrombolysis has been the mainstay of medical therapy, however treatment is limited to a subset of patients and many patients continue to have poor outcomes. Three trials in 2013 investigating the benefit of intra-arterial therapy failed to demonstrate benefit over medical therapy alone. More recently, five trials in 2015 and one in 2016 were completed demonstrating superior outcomes with intra-arterial therapy with improved results attributed to higher and faster rates of recanalization in a select patient population. These trials have introduced a new standard of care in the management of acute ischemic stroke patients. This lecture will address endovascular acute stroke care guidelines that have published based on the data emerging from these trials and will also address the care of patients with large vessel occlusion stroke beyond the guidelines.

## ENDOVASCULAR THERAPY FOR ACUTE ISCHEMIC STROKE. FUTURE DIRECTIONS

TUDOR JOVIN
Associate Professor of Neurology and Neurosurgery at the University of Pittsburgh School of Medicine,
Director, UPMC Stroke Institute, USA
Director, UPMC Center for Neuroendovascular Therapy
President, Society of Vascular and Interventional Neurology (SVIN)

Endovascular therapy for acute stroke due to large vessel occlusion (LVO) is clinical beneficial compared to standard medical therapy but clinical outcomes are still not optimal and therefore the delivery of this treatment is in need of improvement. Three key directions for advancing the field will be addressed in this lecture identified: (1) development of systems of care for ET in large vessel occlusion stroke, (2) development of therapeutic approaches adjunctive to ET, and (3) exploring clinical benefit of ET in patient population insufficiently studied in recent trials.

## THE ROLE OF IMAGING IN PATIENT SELECTION FOR ACUTE STROKE TREATMENT WITH ENDOVASCULAR TECHNIQUES

TUDOR JOVIN
Associate Professor of Neurology and Neurosurgery at the University of Pittsburgh School of Medicine,
Director, UPMC Stroke Institute, USA
Director, UPMC Center for Neuroendovascular Therapy
President, Society of Vascular and Interventional Neurology (SVIN)

Ischemic stroke remains a leading cause of death and disability worldwide. A multitude of recently completed endovascular trials have addressed clinical outcomes and have contributed to elucidating the impact of imaging studies in patient selection. This landmark moment in the history of acute stroke therapy has challenged many of the hitherto held concepts regarding patient selection for reperfusion therapy which provides the impetus to critically analyze the role of imaging in the treatment of acute stroke. In this article, we systematically as a fundamental selection paradigm for aggressive interventions in acute stroke due to large vessel occlusion. This presentation will review the fundamental rationale for using imaging for patient selection and will review key imaging aspects used in most published endovascular stroke trials to date as they relate to clinical outcomes.

## ENDOVASCULAR THERAPY FOR BASILAR ARTERY OCCLUSION

TUDOR JOVIN
Associate Professor of Neurology and Neurosurgery at the University of Pittsburgh School of Medicine,
Director, UPMC Stroke Institute, USA
Director, UPMC Center for Neuroendovascular Therapy
President, Society of Vascular and Interventional Neurology (SVIN)

Basilar artery occlusion (BAO) is devastation condition associated with high mortality (85-95%) if presentation is associated with moderate or severe deficit and recanalization does not occur. Despite better imaging techniques, diagnosis, and therefore treatment, is often delayed. Different therapeutic approaches aiming to reperfuse the brain supplied by the occluded basilar artery are utilized in this condition including intravenous thrombolysis (IVT), mechanical endovascular treatment or bridging approaches but optimal management protocols have not been well established as randomized controlled trials (RCTs) do not exist. Roughly a third of BAO patients reach independent outcome following thrombolysis. Multimodal imaging techniques may be used to choose the best therapeutic option individually. This presentation reviews the clinic-pathological features of basilar artery occlusion, novel imaging modalities that guide therapeutic decisions and different therapeutic options commonly employed in this condition.

## MANAGEMENT OF EXTRACRANIAL CAROTID DISEASE: MEDICAL THERAPY, ENDARTERECTOMY AND STENTING

TUDOR JOVIN
Associate Professor of Neurology and Neurosurgery at the University of Pittsburgh School of Medicine,
Director, UPMC Stroke Institute, USA
Director, UPMC Center for Neuroendovascular Therapy
President, Society of Vascular and Interventional Neurology (SVIN)

Carotid artery stenosis causes approximately 15-20% of ischemic strokes. Advances in medical therapy, surgical technique and stenting has resulted in three viable options for the treatment of carotid stenosis that should be tailored to patient specific characteristics. This lecture represents a review of medical management, carotid artery stenting and carotid endarterectomy as it applies to trials comparing these treatment options.

# UNANSWERED QUESTIONS OR DIFFICULT DECISIONS OF IV. DESOBLITERATION THERAPY

LÁSZLÓ CSIBA
Department of Neurology, Debrecen University, Hungary

1.1. Hemiparesis but not stroke (ca. 8-10% of ivL thrombolysed patients did not suffer from stroke)

- patients with malignant brain tumors had worse outcomes and increased rates of ICH as compared with patients without tumors. In contrast, patients with benign brain tumors had similar outcomes and sICH rates than those without brain tumors.
- ivL in other stroke mimics (multiple sclerosis, atypical migraine, psychogenic hemiparesis, postictal paresis etc.) appears to be safe.

1.2. Rapidly improving hemiparesis, stroke after previous TIA

Patients with mild stroke or rapidly improving stroke symptoms have been excluded from the randomized controlled trials. A metaanalysis confirmed, that rapidly improving stroke was the most common reason to exclude patients from ivL. These patients had bad functional outcomes at discharge. Therefore, the ivL should be considered for patients with mild or improving symptoms if residual deficits are considered as potentially disabling.

Although a prior ischemic stroke within the last 3 months is a contraindication for ivL in patients with stroke, bu a recent TIA in patients presenting with acute stroke should not be excluded from the ivL.

Similarly, prior subclinical lacunar infarction in neuroimaging studies should not be considered automatically as a reason to cancel ivL in patients presenting with stroke, when clinically evident strokes within the past 3 months could be excluded.

1.3. Wake-up stroke

Wake-up stroke is a formal contraindication to ivL as the time of onset cannot be verified. Every seventh of acute strokes is a wake up stroke and most of wake up strokes occur in the morning. Previous and ongoing studies will answer the question which subgroup will have benefit from thrombolysis.

1.4. Concomitant acute or subacute myocardial infarction

ivL in patients with acute ischemic stroke and MI implicates an important risk of cardiac tamponade and should be avoided. Caution should be exercised when administering ivL in patients with acute ischemic stroke and concomitant acute MI.

1.5. Patients on NOAC

ivL might be associated with higher risk of ICH and current guidelines are against thrombolytic treatment in this patient group, unless specific NOAC laboratory test proves no effect of the drug on the coagulation system. Prior use of ACE inhibitors is the most important risk factor for orolingual edema of ivL. Orolingual edema can be treated and ivL should not be discontinued in these patients.

1.6. Patients with symptomatic carotid artery stenosis and other

Prompt revascularization of a symptomatic carotid stenosis after an AIS that received thrombolytic treatment appears to be safe but ideal timing is unknown.

1.7. Patients with brain microbleeds

There are no convincing data that brain microbleeds should influence clinical decision for ivL in acute ischemic stroke. However, clinicians should be aware that high microbleed burden (> 10) might increase the risk of sICH in ivL.

1.8. Artery dissection

IvLysis (ivL) in acute myocardial infarction is problematic with concomitant aortic dissection as it could lead to aortic rupture. Lack of pulse, hypotension and left hemiparesis are often present. Ultrasound, chest X-ray could be helpful for the diagnosis. In contrast, cervical carotid artery dissection is not endangered by artery rupture, with thrombolytic therap but also failed to show a trend towards benefit

1.9. Vascular malformations

- unruptured intracranial aneurysms (UIA),
- UIAs were found in 6-7% of lysis patients and no association with sICH was found. The ivL could be harmless in small asymptomatic aneurysm, but dangerous in large ones. On contrary, the case history should focus on recent thunderclap headache that could signify sentinel bleed. The clinician should focus to the hyperdense MCA sign on CT to exclude superimposed nodular hyperdensity that could be caused by a thrombosed aneurysm. IVT thrombolysis in the presence of an acutely thrombosed aneurysm presenting with symptoms of AIS may be avioded.
- arteriovenous malformations:thrombolytic therapy resulted in sICH in 25% of asymptomatic cerebral cavernous malformation patients (one dozen published observations), therefore one should be cautious with thrombolysis in the CCM patients.

1.10.Literature

Bart M et al. Scientic Rationale for the Inclusion and Exclusion Criteria for Intravenous Alteplase in Acute Ischemic Stroke. Stroke. 2016;47:00-00. DOI: 10.1161/STR.0000000000000086

Davis SM et al. Effects of alteplase beyond 3 h after stroke in the Echoplanar Imaging Thrombolytic Evaluation Trial (EPITHET): a placebo-controlled randomised trial. Lancet Neurol 2008;7:299-309

Jauch EC et al. Guidelines for the early management of patients with acute ischemic stroke: a guideline for healthcare professionals from the American Heart Association/ American Stroke Association. Stroke 2013;44:870-947
Kang DW et al. Reperfusion therapy in unclear-onset stroke based on MRI evaluation
(RESTORE): a prospective multicenter study. Stroke 2012;43:3278-83

Kernan WN et al. Guidelines for the prevention of stroke in patients with
stroke and transient ischemic attack: a guideline for healthcare professionals from the American Heart Association/ American Stroke Association. Stroke 2014;45:2160-236

Ma H et al. A multicentre, randomized, doubleblinded, placebo-controlled Phase III study to investigate EXtending the time for Thrombolysis in Emergency Neurological Deficits (EXTEND). Int J Stroke 2012;7:74-80
Mlynash M et al. Refining the definition of the malignant profile:insights from the DEFUSE EPITHET pooled data set. Stroke 2011;42:1270-5
Thomalla G et al.STIR and VISTA Imaging Investigators. DWI-FLAIR mismatch for the
identification of patients with acute ischaemic stroke within 4.5 h of symptom onset (PRE-FLAIR): a multicenter observational study. Lancet Neurol 2011;10:978-86

Thomalla G et al. WAKE-UP investigators. A multicenter, randomized, double-blind,
placebo-controlled trial to test efficacy and safety of magnetic resonance imaging-based thrombolysis in wake-up stroke (WAKE-UP). Int J Stroke 2014;9:829-36

Tsivgoulis G, Safouris A, Alexandrov AV. Safety of intravenous thrombolysis for acute ischemic stroke in specific conditions. Expert Opin Drug Saf.2015;14(6):845-64.

Tsivgoulis G, Safouris A, Krogias C, Arthur AS, Alexandrov AV. Endovascular reperfusion therapies for acute ischemic stroke: dissecting the evidence. Expert Rev Neurother. 2016 7:1-8.

# BEDSIDE DIFFERENTIAL DIAGNOSIS OF ACUTE DISTURBANCES OF HYPNOID TYPE OF CONSCIOUSNESS

LÁSZLÓ CSIBA
Department of Neurology, Debrecen University, Hungary

2.1. Introduction

The causative diagnosis of consciousness disturbances is one of the most important and difficult clinical tasks. While an incipient renal failure can have vague symptoms, the primary (e.g. commotion) or secondary (e.g. cardiac arrest) insults of the brain provocate a quickdisturbance of consciousness, due to the significant oxygen and energy demand of the brain. Sooner or later, every practicing physician will provide emergency care for a patient suffering from disturbances of consciousness, and will meet the difficulty of the differential diagnosis, too.

2. Hypnoid types of disturbances of consciousness (HDC)

This patient is similar to a sleeping healthy person. In everyday practice these conditions can be divided into two groups:

The patient becomes unconscious very suddenly (usually in seconds). Because the pathological event is transient (such as epileptic seizure or transient cardiacarhythmia), the patient regains his/her awareness quickly.

The possible causes:

a. Central nervous system

a.a. mild head injury resulting only in reversible damage in neurons and axons (concussion without structural impairment).

a.b. epilepsy

a.c psychogenic mechanism

b. Heart:temporary dysfunction of the pump function of the heart (e.g. cardiac arrest) or transient arhythmias.

c. Reflex vasodilation with or without the presence of "b" mechanisms (see also Figure 1.)

The HDC's caused by metabolic dysfunction (e.g. uremia, hypo- or hyperglycemiabarbiturate intoxication etc). belong to an other group, the group of slowly developing HDC, because longer time (minutes, hours, sometimes days) is needed to reach the critical level of blood concentration (e.g. glucose, barbiturate, ammonia) for the dysfunction of the brain. The returning speed of consciousness depends on the normalization of blood concentration of the metabolic factor responsible for the HDC.

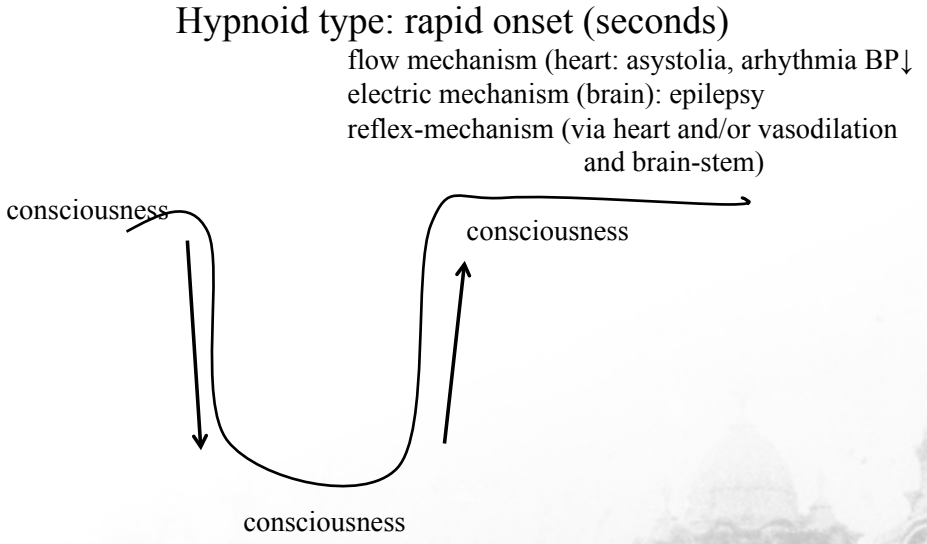


Figure 1. The causes might be in the central nervous system (e.g. epilepsy), heart (arrhythmia, cardiac arrest, temporary dysfunction of pump function), or reflex-mechanism(peripheral vasodilation with consequent ischemia in the central nervous system).

This chapter does not deal with HDCs developing and disappearing quickly (Figure 1.), but with those developing slowly in minutes or hours, and not struck as lightning (Figure 2.).

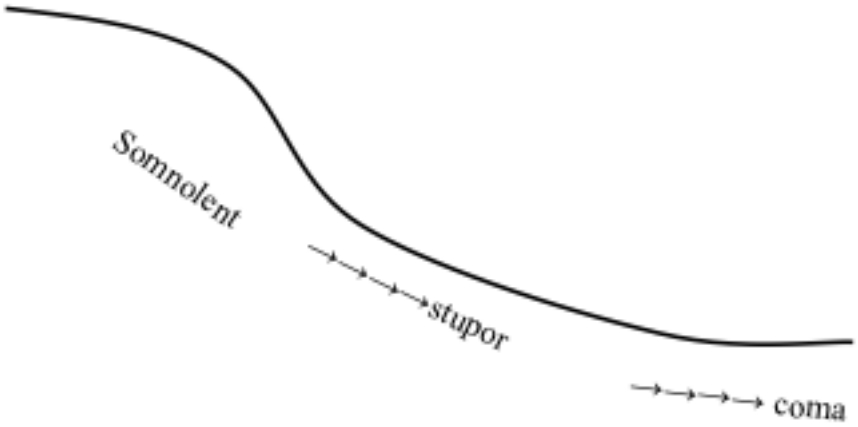



Figure 2. The relatively slowly developing HDC is a frequent finding on ICUs treating intoxicated or metabolic failure (diabetes, liver, kidney etc.) patients or patients with increasing intracranial pressure.

Typical example of slowly developing HDC is the barbiturate intoxication, where drowsiness, deep sleep and coma develop parallel to the drug absorption.

Coma is the most severe stage of hypnoid unconsciousness, in which the patient cannot be woken up and does not response to stimuli. There is no evidence of awareness of self and environment. The patient with continuously closed eyes does not react to external stimuli. The most important symptoms are the absence of spontaneous eye opening and the circadian rhythm of sleep cycles.

The spontaneous or provocated eye opening may return in patients suffering from permanent unconsciousness. The reoccurrence of eye opening and the absence of conscious responses refer to vegetative state (VS, also called as apallic syndrome or coma vigil, incorrectly). According to the American Academy of Neurology the criteria of vegetative state are the following:

1. No evidence of sustained, reproducible, purposeful or voluntary behavioral responses to visual, auditory, tactile or noxious stimuli.

2. No evidence of language comprehension or expression.

3. Return of sleep-wake cycles (periodical eye opening).

The vegetative functions are intact in patients suffering from vegetative state, even responsive or spontaneous movements may occur, but these are always purposeless. They can make sounds or grimace, but inadequately. Patients suffering from vegetative condition are not likely to recover, which is difficult to explain to the family members.

In minimal conscious state (MCS) limited but clearly discernible evidence of self and environmental awareness is demonstrated comparing to the vegetative state. To make the diagnosis of MCS, one or more of the following criteria must be fulfilled:
1. Obeying simple commands
2. Gestural or verbal yes/no responses (regardless of accuracy)
3. Intelligible verbalization

A few examples:
- crying, smiling, laughing in response to the linguistic or visual content of emotional but not to neutral topics or stimuli,
- vocalizations or gestures that occur in direct response to the linguistic content of questions,
- reaching for objects that demonstrates a clear relationship between object location and direction of reach,
- touching or holding objects in a manner that accommodates the size and shape of the object,
- pursuit eye movement or sustained fixation that occurs in direct response to the moving object.

In the latest years, some patients considered being in minimal conscious state for years or decades were reported to have regained the awareness and ability of communication.

2.3. The classification of the severity of hypnoid types of disturbances of consciousness (HDC).
This large group of consciousness disturbances does not involve only the coma,but it contains also the state of somnolence and stupor too. All patients suffering from any type of hypnoid unconsciousness are alike sleeping people, who are healthy otherwise. If not provoked by pain or any other stimulus, the patient is lying with his/her eyes closed.

Somnolence: the patient can be woken up easily, but sleeps away right after being left alone.
Stupor (also known as sopor): the patient seems to be sleeping abnormally deeply, but reflects with motor or verbal responses for motor or verbal stimuli.

Coma (from a greek word meaning deep sleep): The patient does not react for strong pain stimuli, but both the spontaneous breathing and circulation are intact. In the everyday practice, the terms somnolent-stuporous and stuporo-comatose are also widely used for indicating the severity, but cannot be used for quantitative assessments. Instead, we use different coma scales to record the level of consciousness. The lowest possible score of Glasgow Coma scale 3, while the highest is 15 (fully awake person).

Table 1. The Glasgow Coma Scale

| | | |
|---|---|---|
| Eye-opening | Spontaneous | 4 |
| | In response to voice | 3 |
| | In response to painful stimuli | 2 |
| | No response | 1 |
| Motor response | Obeying command | 6 |
| | Localizing response | 5 |
| | Withdraws | 4 |
| | Abnormal flexor response | 3 |
| | Extensor posturing | 2 |
| | No response | 1 |
| Verbal response | Oriented | 5 |
| | Confused conversation | 4 |
| | Inappropriate speech | 3 |
| | Incomprehensible speech | 2 |
| | No verbal response | 1 |

A recommendation published in 2010 compared the scales, which are commonly used to assess the disorders of consciousness. The use of Coma Recovery Scale-Revised (Table 3) is recommended with minimal limitations. The total score range is between 0-23, and the assessment takes 25 minutes.

Table 2. The most frequently used scales in the assessment of consciousness disturbances

CRS-R Coma Recovery Scale-Revised
CLOCS Comprehensive Levels of Consciousness Scale
CNC Coma/Near-Coma Scale
FOUR Full Outline of UnResponsiveness Score
GCS Glasgow Coma Scale
GLS Glasgow-Liege Coma Scale
INNS Innsbruck Coma Scale
LOEW Loewenstein Communication Scale
RLS85 Swedish Reaction Level Scale-1985
SMART Sensory Modality Assessment Technique
SSAM Sensory Stimulation Assessment Measure
WHIM Wessex Head Injury Matrix
WNSSP Western Neuro Sensory Stimulation Profile

Table 3. The Coma Recovery Scale-Revised

1. Auditory function scale
    - 4 Consistent movement to command
    - 3 Reproducible movement to command
    - 2 Localization to sound
    - 1 Auditory startle
    - 0 None

2. Visual function scale
    - 5 Object recognition
    - 4 Object localization: reaching
    - 3 Visual pursuit
    - 2 Fixation
    - 1 Visual startle
    - 0 None

3. Motor function scale
    - 6 Functional object use
    - 5 Automatic motor response
    - 4 Object manipulation
    - 3 Localization to noxious stimulation
    - 2 Flexion withdrawal
    - 1 Abnormal posturing
    - 0 None/Flaccid

4. Oromotor/Verbal function scale
    - 3 Intelligible verbalization
    - 2 Vocalization/Oral movement
    - 1 Oral reflexive movement
    - 0 None

5. Communication scale
    2 Functional: accurate
    1 Non-functional: intentional
    0 None

6. Arousal scale
    3 Attention
    2 Eye opening without stimulation
    1 Eye opening with stimulation
    0 Unarousable

We can find confused patients in every hospital ward who are desoriented in space and time, especially at night hours, but can be contacted, and communicate well (no aphasia!), In these cases desorientation and consequent agitation or aggression dominateand these patients do not suffer from HDC. Delirium due to alcoholism or other causes is characterized by hallucinations and agitation and intense autonomic symptoms. Patients suffering from delirium are also alert and also do not belong to the group of HDC.

2.4. The examination of patients suffering from HDC

The reliable data on medical history and risk factors are very important.
Information should be collected not just about the previous diseases, such as hypertension, diabetes, cardiovascular or hematological disorders, depression, fever, but the medications too. Life habits are very important (medication? alcohol/drug consumption? problems in the private life or at work?)

It should be investigated if the family members experienced any change in the patient's behavior, difficulty in his/her verbal communication and self-expression, or the signs of lightheadedness. Did the patient complain about numbness, visual problems or double vision? Did he/she experience any trauma?Painful stimuli should be used to assess the severity of the consciousness disorder.

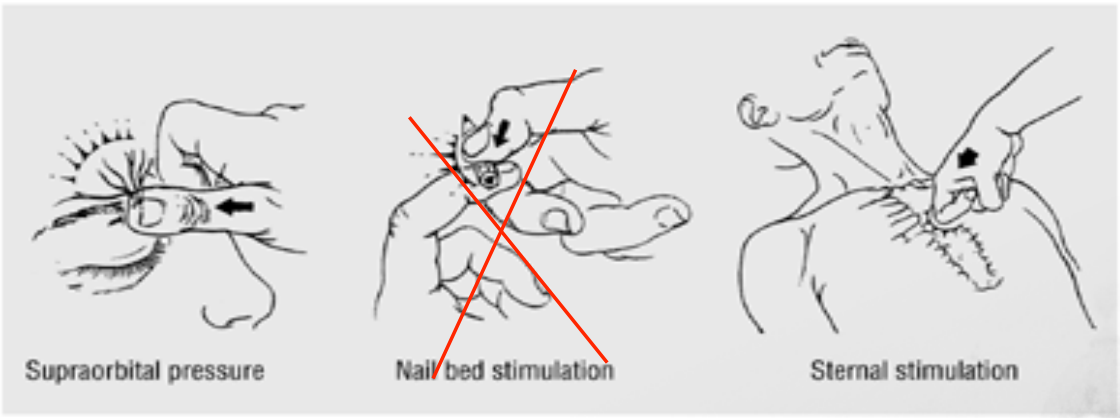



Figure 4. Painful stimuli are applied either on the supraorbital area, sternum or on both mastoid processes. The symmetrical or asymmetrical movements of the extremities can be assessed.

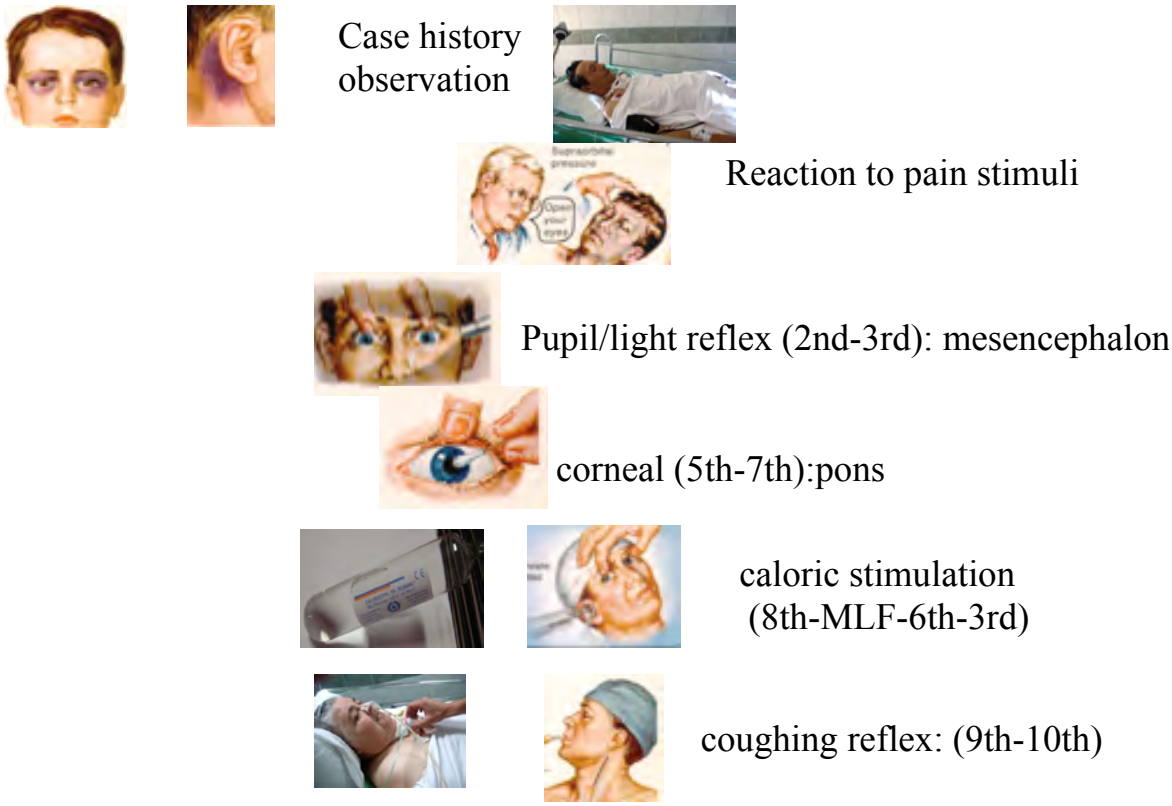



Figure 5. The most important steps of neurological examination in HDC.

2.5. Bedside differential diagnostic considerations of patients suffering from acute HDC.

The normal conscious state requires the intact function of the reticular formation located in the brainstem and the intact function of the supratentorial region activated by the reticular formation. These facts help us to understand the differential diagnosis of consciousness disorders.

Many agents can harm the supratentorial region directly or indirectly, but an isolated brainstem lesion can also cause coma (e.g. occlusion of the basilar artery affecting the brainstem reticular formation). It is essential to understand that whatever damages the supratentorialregion,hypnoid unconsciousness develops only if the pathological process has diffuse/extended effect in the supratentorial area.

(Accepting this postulate it is easy to understand why an acute viral encephalitis or barbiturate intoxication will result in disturbance of consciousness while a large territorial cerebral infarct without mass effect will not alter the consciousness. E.g. always look for other reason of unconsciousness, if CT or MRI reveals focal supratentorial ischemia without mass effect!
With other words: an acute supratentorial focal ischemia or bleeding without mass effect (without midline shift, without increased pressure etc.) will NOT result in HDC, but an acute event with space occupying effect can be accompanied with HCD. Last but not least, all of our statements are valid only for acute events!

A slowly growing tumor or subdural hematoma does not necessarily result in disturbance of consciousness although the CT reveals space occupying/mass effect with midline shift etc.

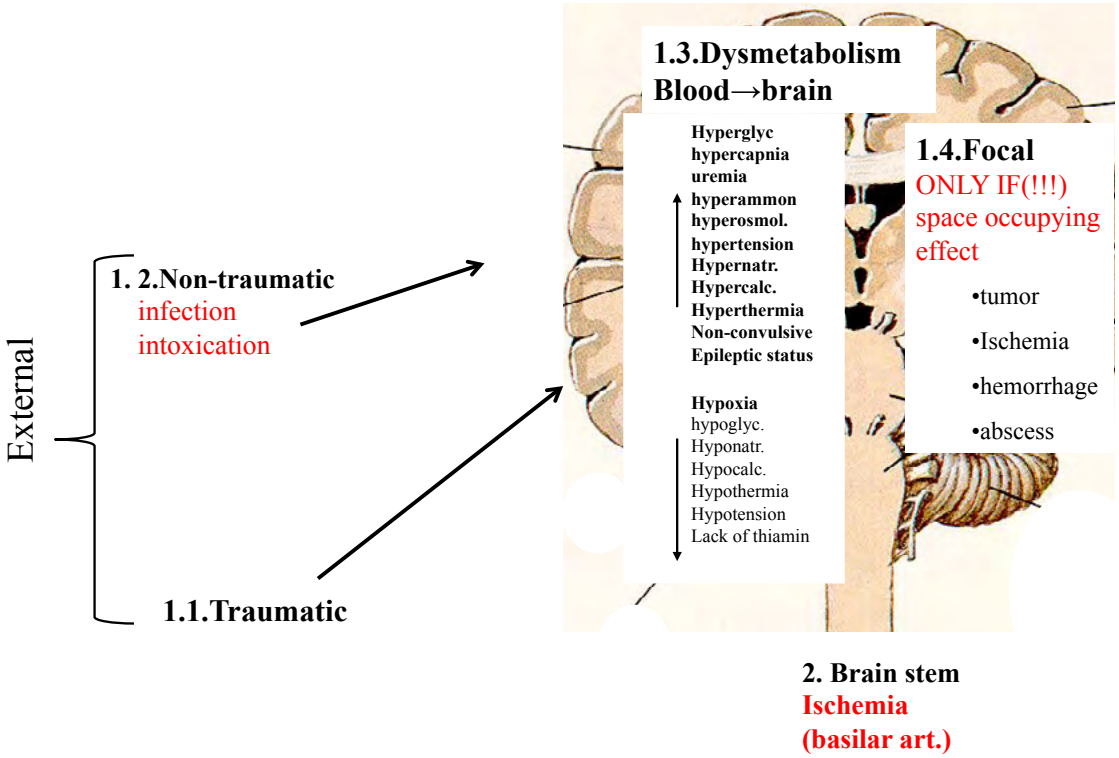



Figure 6. The first group (1.1-1.4) contains those acute external and internal agents, which can cause hypnoid unconsciousness due to the diffuse damage/impacton the supratentorial region. Ischemia of the brainstem or hemorrhage (2.) can cause hypnoid unconsciousness by damaging the reticular formation in the brainstem.

Of course, the mechanism 1.1-1.4.and 2. can be combined.

The diagnostic procedures involving the examination of the relevant agents are summarized in Figure 7.

Now, we can understand that every condition listed in 1.1-1.4 might have negative impact on the function of the whole supratentorial region (even a mild brain concussion, without any apparent CT or MRI abnormality can result in transient loss of consciousness because of the transient colloidal changes of neurons caused by the head trauma (mild and transient but also diffuse impact on the supratentorial region!!).

It is also easy to understand that a viral encephalitis impair diffusely both the gray and white matter, and barbiturate intoxication, electrolyte imbalance, hypoglycemia, hyperglycemia, hormonal defects and hypothermia result inalso diffuse dysfunction of the supratentorial region. Example (epidural hematoma):transient disturbances of consciousness may develop immediately after trauma due to diffuse brain concussion (energy impact) provocating colloidal changes in the neurons. The patient regains his/her consciousness (lucid interval) as the colloidal changes disappear, but after some hours, the increasing intracranial arterial hematoma compresses the ipsilateraland contralateral hemisphere, then HDC develops with hemi-tetraparesis, coma and brain stem herniation.

It is important to emphasize again, that in acute cases the mass effect caused by supratentorial processes correlates well with the severity of consciousness disturbances. If the mass effect evolves very slowly (e.g. in case of tumors or chronic subdural hematoma increasing slowly for weeks), even a significant midline shift or considerable mass effect might remain with intact consciousness!

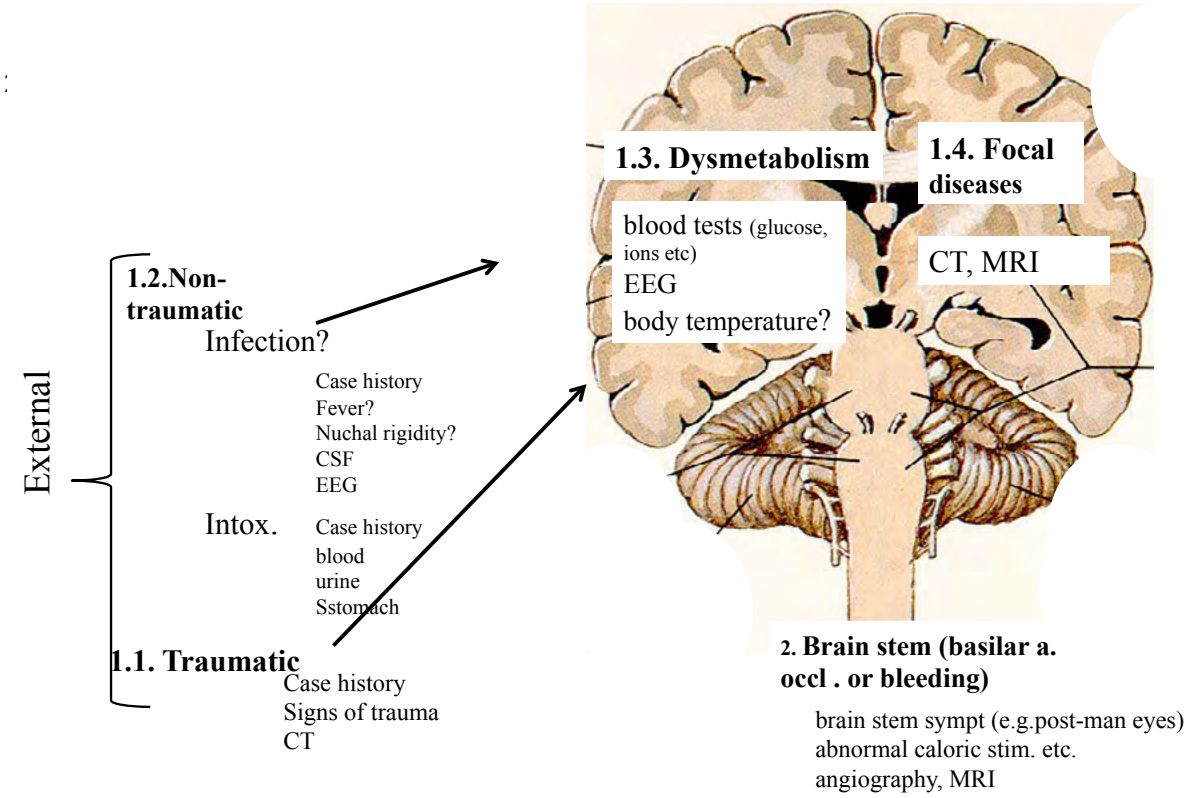



Figure 7. Possible causes and diagnostic steps in HDC patients.

We can identify the cause of HDC (listed in 1.1-1.4 or 2. sections of Figure 6) responsible for the unconsciousness by knowing the medical history and using examinations indicated on Figure 7.

Brainstem lesion is probable the lesion's site if the patient (Fig.7, 1.1--1.4.)
- had no trauma,
- not intoxicated,
- no sign of infection,
- normal labor parameters,
- normal supratentorial CT or MRI finding, or the CT/MRI show lesions without any mass effect.

The anisocoria, diverging eyes, tetraparesis, absence of brainstem reflexes may also suggest the causative role of brain stem, which can be confirmed by basilar artery angiography and brainstem MRI.
The therapy depends on the causative agent, so we do not provide further details about it. In case of basilar occlusion thrombolysis is indicated. If HDC developed due to intoxication, detoxification is needed, etc.

Important! If CT or MRI reveals ischemia or hemorrhage without any mass effect, and the patient has normal conscious state, but hours later he/she shows the signs of any consciousness disturbances, such as somnolence, the hemorrhage is likely to have increased suddenly, or malignant ischemic cerebral edema could have developed, especially if the patient has normal laboratory result, did not experience fever, and did not get any sedatives. In these cases imaging should be performed again!

2.6. Prognosis
The prognosis depends on the causative agent, the patient's age and general condition. According to the survey of the American Academy of Neurology, patients suffering from coma caused by cardiac arrest (hypoxia and

ischemia) are likely to have poor prognosis after 3 days, if any of the followings is present:

- absent pupillary, corneal, coughing reflexes, absent reaction to caloric reflex test, absent or extensor motor responses (evidence A), the presence of seizures or myoclonus status epilepticus (evidence B),
- Bilateral absence of the cortical component of the SSEP predicts a poor outcome (evidence B)
- burst-suppression pattern or generalized epileptiform activity are associated with poor outcome (evidence C).
- serum neuron-specific enolase (NSE, only this marker has verified diagnostic value!) levels >33 µg/L at days 1 to 3 predict poor outcome (evidence B),
- There are insufficient data to support or refute whether the measurement of intracranial pressure, the oxygenisation of the brain, and neuroimaging (MRI, CT)are indicative of poor outcome or not.

2.7. Summary

In case of consciousness disturbances the following examinations are essential:

1. Analysis of the detailed medical history including the information obtained from family members.

2. General physical examination, neurological examination, and the examination of external injuries, including:
- responses to painful stimuli,
- the isocoria of the pupils, eye positions and movements, the presence or absence of pupillary, corneal, and coughing reflexes,

3. The physical examination, the analysis of the imaging and laboratory results may provide the bedside diagnosis of the causative agents listed in Figure 6-7. The treatment of consciousness disturbances can be operative or conservative depending on the causative agents.

2.8.Brain death

We would like to call the attention to some diagnostic criteria of brain death (the irreversible loss of all brain functions above the level of foramen magnum). It is diagnosed if the patient does not have spontaneous breathing, and the pupillary, corneal, coughing reflexes and the caloric reactions are also absent. There are numerous mandatory investigations, here we draw your attention to the apnea-test:

The level of CO2 should be in the range of 38-42 mmHg.
Ten minutes inhalation of 100% oxygen
After disconnection of the ventilator a small catheter with 100% oxygen (6 lit/minute) should be placed into theintubation tube (for adequate tissue oxygen supply).
Blood samples is drawn for testing arterial pCo2 level.
If the repeated sampling with increased CO2 level (60 mmHg or above) cannot return the spontaneous breath, the respiration center of the brain is damaged irreversibly.
The diagnosis of brain death primarily is based on clinical criteria, but we can perform other examinations too, such as imaging techniques, evoked responses of the brainstem, transcranial Doppler, EEG, angiography and scintigraphy.

2.9.Literature

Noseworthy J. H.: Neurological therapeutics. Principles and practice.V.1-2. Martin Dunitz London and New York 2003.
Csiba L. and Fülesdi B. :Sürgősségi ellátás a neurológiában B+V 2000.

Wijdicks EFM et al.Practice Parameter: Prediction of outcome in comatose survivors after cardiopulmonary resuscitation (an evidence-based review). Report of the Quality Standards Subcommittee of the American Academy of NeurologyNeurology 2006;67:203–210

Lerner AJ:The little black book of neurology. 3rd ed. Mosby-Year Book Inc. 1995.

Schwab S, Krieger D, Müllges W, Hamann G and Hacke W: Neurologische Intensivmedizin Springer 1999.

Poeck K, Hacke W: Neurologie 10th ed. Springer 1998.
Olson WH, Brumback RA, Iyer V and GasconG:Handbook of symptom-oriented neurology. 2nd ed. Mosby 1994.
Seel RT et al. Assessment Scales for Disorders of Consciousness: Evidence- Based Recommendations for Clinical Practice and Research. Arch Phys Med Rehabil 2010;91:1795-1813.

# ANCILLARY ULTRASOUND TECHNIQUES USED IN PHARMA TRIALS

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## 3.1. Flow mediated dilation

Many studies proved a prognostic role for endothelial function measurements. Flow-mediated vasodilation was predictive for cardiovascular events in elderly patients [1], in patients with peripheral vascular disease [2], after elective vascular surgery [3], or in patients with coronary artery disease [4]. But the prognostic value of the measurement of endothelial dysfunction is still debated. The measurement of FMD was unable to predict the incidence of hypertension [5], whereas another study demonstrated the predictive value for incident CVD with FMD in thousands of healthy people [6]. Despite the contradictory observations, the therapeutic interventions, which positively influence the risk profile, have a beneficial effect on endothelial function. Not only drugs improve endothelial function in patients with vascular risk factors, but also physical exercise or diet. Numerous techniques exist for measurement of endothelial function (intracoronary infusion of acethylcholin or nitroglycerine, finger plethysmography, direct measurement of circulating endothelium markers etc). but in this syllabus we focus on flow-mediated dilatation measured by ultrasound.

## 3.2. Imaging and measurement of brachial artery dilatation

A stereotactic probe-holding device is suggested for the precise measurement (Fig1.) and the use of a duplex ultrasound is also recommended (both B- mode picture for diameter and pulsed-wave Doppler velocity available).

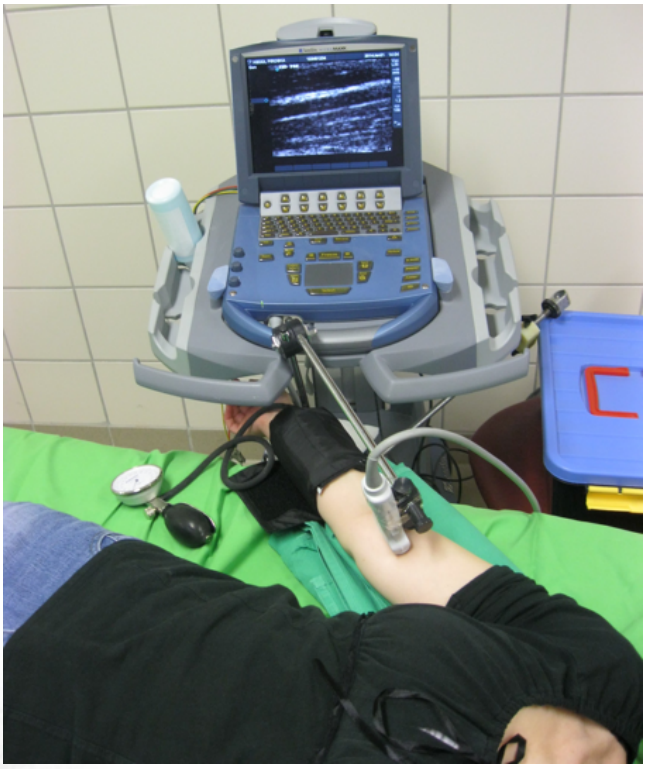

Fig. 1 A stereotactic ultrasound probe-holder is suggested for measurement.

It is difficult to reach the optimal quality with both methods, because the B-mode image needs perpendicular incidence of the ultrasound wave to the vessel orientation, whereas velocity measurements need parallel incidence with the direction of blood vessel flow. A compromise enables that acceptable Doppler shifts are achievable at 60° between the ultrasound beam and the vessel axis, while maintaining good B-mode image. The longitudinal image allows the visualization of the double lines of the artery wall (Fig.2) for precise diameter measurement (less than 0.05 mm) by a special software.

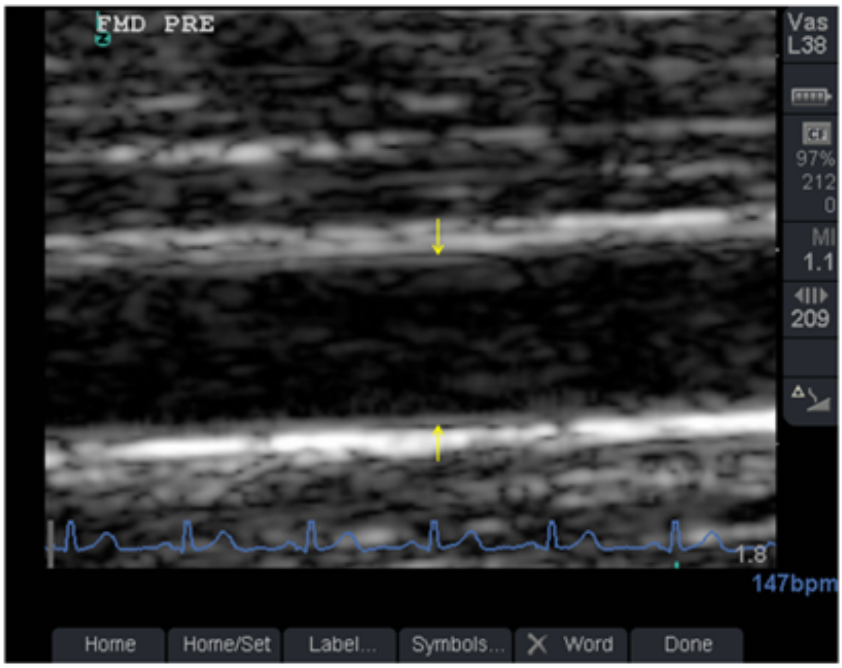


Fig.2. High resolution B-mode image with intima-media.

The peak (measures the fastest moving blood cells in the blood stream center) or mean velocity (intensity weighted, the mean velocity from all of the Doppler shifts measured across the cross section of the vessel) can be used. The two methods can not replace each other in the same study.

Steps of investigation

- Fasting for at least 8 hours. No physical exercise, caffeine, energy drink, alcohol for one day. If the patient can not stop his/her medication the registration of the use/timing of drugs is necessary.
- Rest in a horizontal position with extended arm in a quiet, darkened room for a period of 30 min before testing.
- The investigation should be performed (if repeated) at a similar time of day.
- B-mode images with a probe of 7.5 MHz (or higher) should be used (the same frequency and probe for repeated investigation!)
- 2D color and spectral Doppler imaging
- ECG
- Digital recording
- Automatically deflating pneumatic blood pressure cuff
- Stereotactic probe-holding device recommended

- Blood pressure cuff below the antecubital fossa. Both distal and proximal placement are acceptable, but the distal placement will result in maximal dependence of the vasodilator response on the endothelium and endothelium- produced NO.
- Resting 2D longitudinal image of the brachial artery 2 to 15 cm above the antecubital fossa.
- Baseline diameter must be measured before cuff inflation for a period of at least 30 second.
- Inflate cuff to 50 mm Hg above patient's resting systolic blood pressure (maximum 300 mm Hg) for 5 minutes.
- Measure the diameter before releasing the cuff.
- Deflate the cuff rapidly.
- 2D and Doppler images immediately after deflation and recording every 30 second long as 5 minutes after deflation.

Non-endothel-dependent (NED) vasodilation:

Waiting 20 minutes after FMD measurements.
Baseline 2D image diameter and velocity measurement.
Nitroglycerin to adults (usually 300 microgramm).
Images should be recorded every 30 sec up till 3 minutes after the dose.
The peak velocity of ultrasound measurement is recommended for analysis.
Automated mathematical algorithms could be used to calculate the peak diameter.

The simultaneous velocity and diameter measures may decrease B-mode image resolution (and the precise measurement). Therefore, measuring the first minute of the shear-stress stimulus may provide valid data, but the optimal approach would be a continuous detection with high resolution Doppler and B-mode images to the time of peak diameter for the calculation of shear.

Calculations:

- %FMD= (Dinfl - Dbase)/Dbase X 100 .
- Reactive hyperemia =(Vel infl – Vel base)/Vel base x 100

3.3. Future directions

Because the endothelial dysfunction is the summarized results of the effect of one or more vascular risk factor, the future research should decide if the investigation of endothelial function might be a better predictor for vascular events than the present prognostic factors. There are promising observations about the prognostic value of FMD measurement. The brachial artery FMV may predict vascular risk, but its incremental predictive value to clinical prognostic models has not been established. A metaanalysis [12], and a recent prospective study found brachial artery median FMD independently predicts long-term adverse vascular events in healthy subjects with no apparent heart disease in addition to those derived from traditional risk factor assessment. [13] In 13 of 15 studies of the metaanalysis the predictive power of FMV has been confirmed.

But it is debated, if endothelial function should be regularly detected in low risk patients. To answer this question, we need different groups of patients with endothelial dysfunction and with different pharmacological interventions lifestyle modifications and long term follow up.

The measurement of endothelial function can detect responders from nonresponders to therapy. Those patients whose endothelial function doesn't improve after therapeutic interventions are at a high risk for further events. It means, that therapy can be guided by repeated endothelial function measurements, but we need more studies to answer the

3. 4. IMT measurement

Carotid wall alterations precede cardiovascular clinical events. The morphological damage of arterial walls can be visualized by B-mode ultrasonography.

The IMT (intima-media thickness) is a double-line pattern visualized by ultrasound on the walls of the CCA or ICA in a longitudinal image. Two parallel lines, which consist of the leading edges of two anatomical boundaries, form it: the lumen-intima and media-adventitia interfaces (Fig.2). Plaques are focal structures encroaching into the arterial lumen of at least 0.5 mm or 50% of the surrounding IMT value, or demonstrates a thickness >1.5 mm as measured from the intima-lumen interface to the media-adventitia interface (7). All vascular risk factors contribute to increased IMT thickening but intermediate stages between increasing IMT and atherosclerotic plaque formation cannot clearly be differentiated by ultrasound.

Technical consideration

Carotid arterial wall investigation may include the common, internal or bulb segments of the carotid artery (Fig.3).

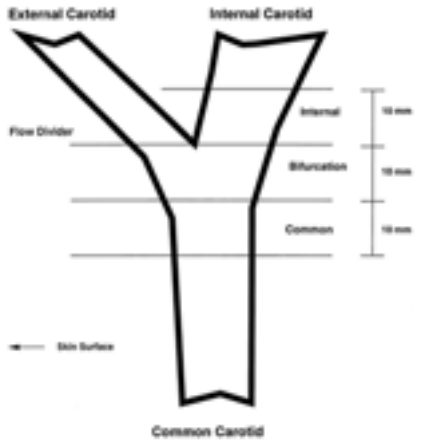


Fig. 3. IMT measurement is possible on the common carotid artery (suggested), bifurcation and internal carotid artery.

Standard equipment includes a high-resolution B-mode system operating in the black and white mode, preferentially with linear ultrasound transducers at frequencies >7 MHz.

Arterial wall segments should be assessed in a longitudinal view, strictly perpendicular to the ultrasound beam. Both walls should be clearly visualized in order to achieve diameter measurements. The optimal diameter should be obtained during diastole by automatic cine-loop detection or by looking for the minimal diameter during the cardiac cycle (7).

Lateral probe position is recommended as it offers the best resolution in the midfield and longitudinal and cross-sectional views are required to visualize focal atherosclerosis (7).

Plaque acquisition should be done along the carotid tree, in longitudinal and cross-sectional views.

3.5. Measurement of IMT

Measurement of IMT should occur within a region free of plaque with a clearly identified double-line pattern. [8–10].

- IMT should be measured preferably on the far wall of the CCA at least 5 mm below its end.
- Along 10 mm length of a straight arterial segment, a high-quality image acquisition is required for reproducible serial measurements.
- Plaque: Maximal thickness requires demonstration from 2 different angles of insonation, in longitudinal and cross-sectional views.

- Edge detection systems results in higher accuracy of IMT [11].
- Manual measurements are more observer dependent than semi-automatic systems. Automated systems can provide the mean maximal value of 150 measurements performed on a 10-mm segment of CCA instantaneously.
- CCA inter-adventitial and intraluminal diameters must also be measured because IMT depends on arterial diameter.
- IMT measurements include the mean, maximum, composite measures from both sides and different arterial sites.
- Mean IMT values averaged across the entire distance are less susceptible to outliers, whereas the maximal IMT may reflect more advanced stages with focal thickening or plaque formation.
- IMT values from the left and right side can be averaged although there is a significant difference between the left and right CCA IMT, with higher values on the left side [12].
- Each vascular laboratory should elaborate its age-dependent control values and evaluate the intra- and interobserver variability.

3.6. Clinical and Research use

Numerous international guidelines recommend the use of IMT for the assessment of cardiovascular risk:

- ACC/AHA recommends ('reasonable to perform') in individual at intermediate coronary heart disease risk [13].

The American Society of Echocardiography [14] and the Society of Atherosclerosis Imaging and Prevention [15] published criteria.

CIMT and plaque presence are recommended for the initial detection of CHD risk in asymptomatic patients:

- at intermediate risk
- in the setting of 2 or more NCEP risk factors
- with metabolic syndrome
- in the setting of a family history of premature coronary heart disease
- with a known coronary artery calcification score of zero and

Framingham Risk Score 11–20%.

Several guidelines demonstrate that carotid artery B-mode ultrasound imaging is safe, noninvasive and relatively inexpensive allowing to assess subclinical atherosclerosis [33–35] in asymptomatic persons >45 years old and could add incremental information to traditional risk factor assessment [36–39].

CCAIMT 'normal values' in the absence of plaque should help to characterize populations at intermediate risk.

3.7. IMT in Research

IMT and plaque measurements including maximal or mean IMT, plaque thickness, area and volume, and plaque score may all be useful as imaging outcomes for observational studies (from six months till years). Not only the IMT progression but also the regression could be demonstrated with appropriate pharmacological interventions and positive correlation found between the IMT changes and clinical event. All these procedures and choices can reduce measurement variability, which is a key parameter for a high-quality study, statistical power and sample size determination. Plaque presence demonstrates a higher risk and therefore overrides IMT predictive values. However, IMT without plaque remains a significant marker of an increased risk of vascular events and significantly predicts plaque occurrence. The continuity of vascular wall changes is best monitored in CCA IMT studies, different from discontinuous focal lesions (plaque) which are characteristic of atherosclerotic disease. Therefore, the distinction between IMT and plaque must be clearly specified in the scanning protocols.

## 3.8. Literature


1. Yeboah J et al. Brachial flow-mediated dilation predicts incident cardiovascular events in older adults: the Cardiovascular Health Study. Circulation. 2007;115:2390–7.
2. Brevetti G et al. Endothelial dysfunction and cardiovascular risk prediction in peripheral arterial disease:additive value of flow-mediated dilation to ankle-brachial pressure index. Circulation. 2003;108:2093–8.
3. Gokce N et al. Risk stratification for postoperative cardiovascular events via noninvasive assessment of endothelial function: a prospective study. Circulation. 2002;105:1567–72.
4. Chan SY et al. The prognostic importance of endothelial dysfunction and carotid atheroma burden in patients with coronary artery disease. J Am Coll Cardiol. 2003;42:1037–43.
5. Shimbo D et al. Endothelial dysfunction and the risk of hypertension: the multi-ethnic study of atherosclerosis. Hypertension. 2010;55:1210–6.
6. Yeboah J et al. Predictive value of brachial flow-mediated dilation for incident cardiovascular events in a population-based study: the multi-ethnic study of atherosclerosis. Circulation. 2009;120:502–9.
7. Touboul PJ et al. Mannheim Carotid Intima-Media Thickness and Plaque Consensus (2004–2006–2011): Cerebrovasc Dis. 2012 ; 34(4): 290–296.
8. Greenland P et al. ACCF/AHA guideline for assessment of cardiovascular risk in asymptomatic adults: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. 2010; 56:e50–e103.
9. Stein JH et al. Use of carotid ultrasound to identify subclinical vascular disease and evaluate cardiovascular disease risk: a consensus statement from the American Society of Echocardiography Carotid Intima-Media Thickness Task Force.Endorsed by the Society for Vascular Medicine. American Society of Echocardiography Carotid Intima-Media Thickness Task Force. J Am Soc Echocardiogr. 2008; 21:93–111.
10. Society of Atherosclerosis Imaging and Prevention, Developed in collaboration with the International Atherosclerosis Society. Appropriate use criteria for carotid intima thickness testing. Atherosclerosis. 2011; 214:43–46.
11. Lorenz M et al. Is carotid intima media thickness useful for individual prediction of cardio vascular risk? Ten years results from the Carotid Atherosclerosis Progression Study (CAPS). Eur Heart J. 2010; 31:2041–2048.
12. Aguilar-Shea A et al. Carotid intima-media thickness as a screening tool in cardiovascular primary prevention. Eur J Clin Invest. 2011; 41:521–526.
13. Touboul PJ et al. Correlation between the Framingham risk score and intima media thickness: The Paroi Arterielle et Risque Cardio-vasculaire (PARC) study. Atherosclerosis. 2007; 192:363–369.
14. Nambi V, Chambless L, Folsom AF, et al. Carotid intima-media thickness and presence or absence of plaque improves prediction of coronary heart disease risk: The ARIC (Atherosclerosis Risk in Communities). Study J Am Coll Cardiol. 2010; 55:1600–1607.


## INTIMA-MEDIA THICKNESS MEASUREMENT AS AN OBJECTIVE NON-INVASIVE MEASUREMENT TOOL OF CARDIOVASCULAR RISK

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Intima-media thickness (IMT) provides a surrogate end point of cardiovascular outcomes in clinical trials evaluating the efficacy of cardiovascular risk factor modification. The participants will learn the method of the IMT measurement and the possible mistakes and limitations in hands-on training session. The possible applications are: prediction of the future risk of stroke/AMI, evaluation of the (single/combined) effect of risk factors (age, gender, race, HT, DM, HLP, smoking, etc.), studies of new therapies or lifestyle modification on arteriosclerosis, research of potential new risk factors, evaluation of the effect of genetic factors on the arteriosclerosis, use of carotid IMT measurements in young, positioning of carotid IMT trials in the development phase of new pharmacological agents, risk stratification. Potential use the carotid IMT in clinical area is to screen/rule out existing disease, evaluate therapeutic benefit etc. Standardized methods will foster homogenous data collection and analysis, improve the power of randomized clinical trials incorporating IMT measurement.

## TCCD EXAMINATION AND ITS PITFALLS

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Transcranial color-coded duplex ultrasonography (TCCS) enables the visualization of basal cerebral arteries through the acoustic windows of the intact skull by color-coding of blood flow velocity. TCCS is an important non-invasive neuroimaging method due to its excellent time resolution. In the hands-on training session the proper examination technics, the clinical aspects and the possible pitfalls are presented. In addition to the diagnostics of intracranial vascular disease, this technique is valuable in intensive care and stroke units, e.g. for follow-up examinations in vasospasm after subarachnoid haemorrhage, for brain death and for intraoperative monitoring as well. In difficult anatomical conditions, the application of echo contrast agents can improve the diagnostic reliability of the examination.

## OPTIC NERVE EXAMINATION AS THE SIGN OF ELEVATED INTRACRANIAL PRESSURE

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Elevated intracranial pressure (ICP) is seen for example in head trauma, intracranial tumours, stroke, hydrocephalus, meningitis/encephalitis, metabolic encephalopathy. Intractable elevated ICP can lead to death or devastating neurological damage either by reducing cerebral perfusion pressure (CPP) and causing cerebral ischemia or by compressing and causing herniation of the brainstem or other vital structures. Prompt recognition is crucial in order to intervene appropriately. The new non-invasive ICP evaluation method, the optic nerve sheath diameter (ONSD) measurement presented in the hands-on training session.

# PERIPHERAL NERVE/MUSCLE ULTRASOUND EVALUATION AS A SPECIAL TECHNICS SUPPORTING OF EMG DIAGNOSIS AND BOTULINUM TOXIN THERAPY

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Because of the recent technical developments and advances in high-resolution imaging, ultrasound has become more important for diagnosis of muscle and peripheral nerve disease. 12-20 MHz transducer frequencies are suitable for more superficial, and 8-12 MHz frequencies for deeper nerve and muscle structures. The muscle and nerve structures of the extremities are demonstrated in hands-on training sessions. The possible future applications are: analysis of muscle diseases, peripheral neuropathies and lesions of peripheral nerves, evaluation before nerve blocks, ultrasound controlled botulinum toxin injections and ultrasound guided lumbar puncture procedures.

# NOTES

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