

## FOREWORD

Stroke remains the third most common cause of death in the world, and the leading cause of death in the Republic of Croatia. In addition, stroke is also the leading cause of disability in Croatia and worldwide. We are fully aware of the fact that not only older age groups are affected by stroke, as individuals of the most productive age have recently been ever more involved, making stroke a great health as well as economic problem. Epidemiologic data from the industrialized countries have shown a decreasing trend in the stroke morbidity and mortality over the last decades of the past century, which could be directly attributed to the preventive measures implemented in these countries. In contrast, data for Croatia point to an increase in the stroke morbidity and mortality. A similar unfavorable tendency in the incidence of stroke has also been recorded in other Central and East European countries as well as in a majority of developing countries. Therefore, an 'epidemic' of stroke has been anticipated to occur in the decades to come. It has been demonstrated that the management of stroke patients on appropriately equipped wards (stroke units) significantly reduces the mortality and disability, whereas additional disability reduction can be achieved by early rehabilitation of stroke patients. For the first time in history, an efficacious therapy for ischemic stroke has become available with the use of recombinant tissue plasminogen activator, however, only within 3 hours from the onset of stroke.

Unfortunately, not all new concepts have yet been generally accepted and frequently are not used in practice. It is therefore necessary to address both medical professionals and the population at large to make them aware that stroke is preventable by the consistent use of all methods of primary and secondary prevention. Also, it should be repeated over and over that stroke is an emergency condition which requires prompt medical treatment in appropriately equipped units.

The intention of the First Congress of the Croatian Society for Neurovascular Disorders of the Croatian Medical Association, and Second Congress of the Croatian Society for Stroke Prevention, to be held on October 16-19, 2002, in Osijek, Croatia, is to present the latest achievements in the fields of epidemiology, prevention and diagnosis of stroke, and of treatment and rehabilitation of stroke patients. I do hope indeed that presentations in the form of plenary lectures and posters will help in adopting and spread of the concepts according to which stroke is an emergency medical condition, and that it can be both prevented and treated. Only the joint, concerted and persistent actions of all of us will result in the reduction of stroke prevalence, and so eliminate stroke from the ignominious leading position on the list of the causes of mortality in Croatia.

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## PREDGOVOR

Moždani udar je i nadalje treći uzrok smrtnosti u svijetu, a prvi uzrok smrtnosti u Republici Hrvatskoj. Uz to, moždani udar je prvi uzrok invalidnosti u nas i u svijetu. Svjedoci smo i činjenice da moždani udar više ne zahvaća samo starije dobne skupine; zadnjih godina od moždanog udara obolijevaju sve češće i bolesnici u najproduktivnijim godinama života, što ga čini velikim kako zdravstvenim tako i ekonomskim problemom. Epidemiološki podaci iz zapadnih zemalja pokazuju smanjivanje morbiditeta i mortaliteta od moždanog udara u zadnjim desetljećima prošloga stoljeća, što je izravna posljedica preventivnih aktivnosti. Nasuprot tome, podaci za Hrvatsku pokazuju porast morbiditeta i mortaliteta od moždanog udara. Sličan nepovoljan trend porasta učestalosti moždanog udara bilježi se i u ostalim državama srednje i istočne Europe, kao i u većini zemalja u razvoju, pa se u dolazećim desetljećima predviđa "epidemija" moždanog udara. Dokazano je da se zbrinjavanjem bolesnika u primjereno opremljenim odjelima (jedinice za moždani udar - *stroke units*) značajno smanjuju mortalitet i invalidnost, a rano započetom rehabilitacijom bolesnika s moždanim udarom moguće je dodatno smanjiti invalidnost. Po prvi puta u povijesti na raspolaganju nam je učinkovito liječenje ishemijskog moždanog udara primjenom rekombiniranog tkivnog aktivatora plazminogena, ali samo unutar prva tri sata od nastanka moždanog udara.

Nažalost, sve navedene spoznaje još uvijek nisu opće prihvaćene i često se u praksi ne primjenjuju. Stoga je nužno potrebno među zdravstvenim djelatnicima i u pučanstvu širiti spoznaju da se moždani udar može spriječiti dosljednom primjenom svih metoda primarne i sekundarne prevencije. Također, treba stalno naglašavati da je moždani udar hitno medicinsko stanje koje zahtijeva hitan zdravstveni tretman u primjereno opremljenim jedinicama.

Prvi kongres Hrvatskoga društva za neurovaskularne poremećaje Hrvatskoga liječničkog zbora i Drugi kongres Hrvatskoga društva za prevenciju moždanog udara, koji će se održati u Osijeku od 16. do 19. listopada ove godine, ima za cilj prikazati najnovija dostignuća u području epidemiologije, prevencije i dijagnostike moždanog udara, liječenja i rehabilitacije bolesnika s moždanim udarom. Nadam se da ćemo radom u okviru plenarnih predavanja i kroz postere na ovom kongresu pomoći u prihvaćanju i širenju spoznaja da je moždani udar hitno medicinsko stanje i da se moždani udar može spriječiti i liječiti. Samo zajedničkim, upornim i dugotrajnim akcijama svih nas možemo postići smanjivanje učestalosti moždanog udara i na taj način ukloniti moždani udar s neslavnog prvog mjesta uzroka smrtnosti u Hrvatskoj.

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## STROKE – DIAGNOSTIC AND THERAPEUTIC GUIDELINES

## MOŽDANI UDAR – SMJERNICE U DIJAGNOSTICI I TERAPIJI

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Now, when the decade of brain has been ended, stroke still remains the third cause of death in the world and the leading cause of death in the Republic of Croatia. Also, stroke is the leading cause of disability both in the world and in Croatia. Recently, stroke appears to pose an ever growing health as well as economic problem due to an increasing prevalence of stroke in the most productive age groups.

Epidemiologic data from western countries point to a decrease in the stroke morbidity and mortality rates over the last decades of the past century, which has been directly attributed to efficient preventive activities. In contrast, however, data for Croatia show an increase in the stroke morbidity and mortality rates.

Prevention remains the best approach to stroke. The objective of preventive measures is to reduce the risk of stroke by influencing the risk factors for stroke. The most common risk factors for stroke include inappropriate dietary habits, alcohol consumption, cigarette smoking, inadequate physical activity, hypertension, diabetes mellitus, elevated serum cholesterol, myocardial infarction, atrial fibrillation, and carotid stenosis.

In the diagnosis of cerebral circulation pathology, doppler sonography has become an indispensable tool. Extracranial color doppler and transcranial doppler allow for rapid evaluation of the patient's cerebrovascular status and visualization of various cerebrovascular pathologic conditions. These examinations are noninvasive, can be repeated without patient risk exposure, and can be performed at bedside, thus having become the main diagnostic method in primary prevention of cerebrovascular diseases.

Nakon završene dekade mozga moždani udar je i nadalje treći uzrok smrtnosti u svijetu, a prvi uzrok smrtnosti u Republici Hrvatskoj. Moždani udar je prvi uzrok invalidnosti u nas i u svijetu. Zadnjih godina od moždanog udara sve češće obolijevaju i bolesnici u najproduktivnijim godinama života, što ga čini sve većim kako zdravstvenim tako i ekonomskim problemom. Epidemiološki podaci iz zapadnih zemalja pokazuju smanjivanje morbiditeta i mortaliteta od moždanog udara u zadnjim desetljećima prošloga stoljeća, što je izravna posljedica preventivnih aktivnosti. Nasuprot tome, podaci za Hrvatsku pokazuju porast morbiditeta i mortaliteta od moždanog udara. Prevencija je još uvijek najbolji pristup moždanom udaru. Cilj prevencije je smanjiti rizik nastanka moždanog udara djelovanjem na čimbenike rizika. Najčešći čimbenici rizika uključuju neprijemnu prehranu, konzumiranje alkohola, pušenje, smanjenu tjelesnu aktivnost, hipertenziju, šećernu bolest, povišene vrijednosti kolesterola u serumu, infarkt miokarda, atrijsku fibrilaciju i karotidnu stenozu. U dijagnostici patologije moždane cirkulacije doplerska je sonografska dijagnostika postala nezaobilaznom metodom. Ekstrakranijski obojeni dopler i transkranijalni dopler omogućuju brzu procjenu cerebrovaskularnog statusa bolesnika te prikaz raznih patoloških stanja na krvnim žilama. Pretrage su neinvazivne i mogu se ponavljati bez rizika za bolesnika, čime su postale glavnom dijagnostičkom metodom u primarnoj prevenciji cerebrovaskularnih bolesti, a pogodne su i za primjenu uz bolesnički krevet. Terapija ishemijskog moždanog udara zasniva se na antiagregacijskom liječenju koje se preporuča osobama s čimbenicima rizika, nakon tranzitome ishemijske atake (TIA) ili moždanog udara, a primjenjuje se i kod akutnog ishemijskog moždanog udara,

The treatment of ischemic stroke is based on antiaggregation therapy that is recommended for patients with risk factors after transient ischemic attack (TIA) or stroke, and is also used in acute ischemic stroke, whereas anticoagulant therapy is indicated in specific cases of acute ischemic stroke, and in secondary prevention in the presence of some cardiac diseases (atrial fibrillation). In symptomatic patients with significant carotid arterial stenosis, surgical procedure is therapy of choice.

Thrombolysis (rtPA) has for several years now been used in many western countries in the management of acute ischemic stroke. The treatment is performed strictly following the established protocol, because any modification is associated with a high risk of complications. Although thrombolysis can only be done in a small proportion of patients, it clearly shows that stroke is amenable to treatment and that the need of prompt reaction by the patient, his environment and medical personnel should be emphasized. In addition to the latest research into thrombolysis support by continuous transcranial Doppler (TCD) monitoring, numerous studies aimed at emergency intervention on the penumbra have been under way.

It has been demonstrated that stroke mortality and disability rates can be considerably reduced by the management of stroke patients in appropriately equipped units (stroke units), however, such a concept obviously entails the need of health care restructuring. Stroke should be recognized as an emergency state that requires emergency transportation to an appropriately equipped institution.

In spite of the advances made in the care of stroke patients, they frequently suffer severe lesions and functional restrictions of movement and perception. Rehabilitation is crucial in the care of stroke patients. The grade of disability can be additionally reduced by early rehabilitation. Although rehabilitation programs will not modify the patient's neurologic deficit, they may considerably contribute to the patient's regaining independence. Rehabilitation should be performed by a multidisciplinary team of professionals, which should also include the patients and their family members.

Upon the completion of the decade of brain, we can state that neurology has achieved considerable advancements in the care of stroke patients. Considering the many researches that are under way, the future will hopefully bring even greater steps forward.

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dok se antikoagulantna terapija indicira u posebnim slučajevima akutnog ishemijskog moždanog udara, a u sekundarnoj prevenciji nalazi mjesto kod određenih srčanih bolesti (atrijska fibrilacija). Kod simptomatskih bolesnika sa značajnom stenozom karotidnih arterija kirurški je zahvat terapija izbora. Unazad nekoliko godina u brojnim zapadnim zemljama u liječenju akutnog ishemijskog moždanog udara primjenjuje se tromboliza (rtPA). Liječenje se provodi po točno određenom protokolu, jer svako odstupanje donosi velik rizik komplikacija. Mada je trombolizu moguće provesti samo u malobrojnih bolesnika, ona je putokaz da terapija ishemijskog moždanog udara postoji i da treba naglašavati potrebu promptne reakcije bolesnika, njegove okoline i medicinskog osoblja. Uz najnovija istraživanja usmjerena ka potpomaganju trombolize pomoću kontinuiranog monitoriranja transkranijalnim doplerom (TCD-om) provode se brojna istraživanja koja imaju za cilj urgentno djelovati na penumbri. Dokazano je da se zbrinjavanjem bolesnika u pri-mjereno opremljenim odjelima (jedinice za moždani udar - *stroke units*) čak i bez primjene trombolize značajno smanjuje smrtnost i invalidnost. Stoga je neophodna reorganizacija medicinske službe kako bi se moždani udar shvatio kao hitno stanje koje zahtijeva hitan transport u primje-reno opremljenu ustanovu.

Usprkos napretku u zbrinjavanju bolesnika s moždanim udarom bolesnici nakon preboljelog moždanog udara vrlo često imaju teška oštećenja i funkcionalna ograničenja kretanja i percepcije. Rehabilitacija je ključna u zbrinjavanju bolesnika s preboljelim moždanim udarom. Rano započetom rehabilitacijom moguće je dodatno smanjiti invalidnost. Iako rehabilitacijski programi ne mijenjaju neurološki deficit bolesnika, mogu značajno pridonijeti osamostalivanju bolesnika. Rehabilitaciju bi trebao provoditi multidisciplinarni tim stručnjaka. Bolesnici i članovi njihovih obitelji moraju biti uključeni u rehabilitacijski tim. Nakon završene dekade mozga možemo reći da neurologija bilježi značajan napredak u zbrinjavanju bolesnika s moždanim udarom. S obzirom na mnogobrojna istraživanja koja su u tijeku, za nadati se je da će budućnost donijeti još veće iskorake.

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## EPIDEMIOLOGY OF STROKE EPIDEMIOLOGIJA MOŽDANOG UDARA

### EPIDEMIOLOGY OF STROKE EPIDEMIOLOGIJA MOŽDANOG UDARA

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The World Health Organization defines stroke as a “rapid development of clinical signs of focal (or global) impairment of brain functions, with symptoms lasting for 24 hours or longer, or leading to death, without any other obvious cause apart from the signs of vascular damage”. In clinical practice, the classification taking the pathoanatomical and pathophysiological parameters in consideration, and differentiating hemorrhagic stroke that occurs in 15% - 20% and ischemic stroke accounting for 80% - 85% of cases, has been widely accepted. Hemorrhagic stroke is further divided into the subtypes of intracerebral hemorrhage of typical or atypical localization, accounting for some 15%, and subarachnoid hemorrhage (SAH), occurring in some 5% of all stroke cases. Ischemic stroke is divided into the following subtypes: thrombotic, embolic, and hemodynamic stroke. According to the International Classification of Diseases, cerebrovascular diseases are categorized in a similar way, with the following subgroups encoded I60 - I69: SAH, intracerebral hemorrhage, other nontraumatic hemorrhages, cerebral infarction caused by extracerebral or intracerebral occlusion, and nonspecific stroke. Recently, a practical TOAST classification of ischemic stroke has been widely used, differentiating the following categories: large blood vessel infarcts, lacunar infarcts, cardioembolic infarcts, infarcts due to other causes, and infarcts of unknown cause.

It has been estimated that about 4 million people suffer stroke in the world *per* year, some 570,000 of these in

Svjetska zdravstvena organizacija definira moždani udar (MU) kao “naglo razvijanje kliničkih znakova fokalnog (ili globalnog) poremećaja moždanih funkcija, sa simptomima koji traju 24 sata ili duže, ili vode k smrti, bez drugog jasnog uzroka, osim znakova oštećenja krvnih žila”. U kliničkom radu široko je prihvaćena klasifikacija koja uzima u obzir patološko-anatomske i patofiziološke parametre, te razlikuje hemoragijski moždani udar (HMU) koji se javlja u 15%-20% i ishemijski moždani udar (IMU) koji čini 80%-85% slučajeva. Podtipovi HMU-a su: intracerebralna hemoragija tipične ili atipične lokalizacije, koja predstavlja oko 15% te subarahnoidna hemoragija (SAH) koja predstavlja oko 5% slučajeva MU-a. Podtipovi IMU-a su: trombotski, embolijski i hemodinamski udar. Međunarodna klasifikacija bolesti razvrstava cerebrovaskularne bolesti (CVB) na približno isti način, navodeći pod šiframa I 60-I 69 podskupine: SAH, intracerebralno krvarenje, ostala netraumatska krvarenja, cerebralni infarkt uzrokovan ekstracerebralnom ili intracerebralnom okluzijom, te nespecificirani moždani udar. Praktična je i u zadnje vrijeme u široj uporabi klasifikacija IMU-a TOAST koja razlikuje sljedeće kategorije: infarkte velikih krvnih žila, lakunarne infarkte, kadioembolijske infarkte, infarkte koji su posljedica drugih uzroka, te infarkte nepoznatog uzroka. Procjenjuje se da u svijetu na godinu od MU-a oboli oko 4 milijuna ljudi. Od toga na Europu otpada otprilike 570.000, a na Sjedinjene Američke Države oko 500.000 oboljelih. U prikazu incidenije MU-a obično se rabe dobno standardizirane stope (*age-*

Europe and 500,000 in the United States of America. On presenting the incidence of stroke, the age-standardized incidence rates are generally used. International epidemiologic studies show the incidence rates to rise exponentially with age, ranging between 0.3‰ in the third and fourth decade of life to up to 30‰ in the eighth and ninth decade of life, or 1-2‰ on an average.

The prevalence of stroke in the world varies between 5‰ and a few percentage. It is estimated that approximately one third of stroke patients die, one third suffer severe neurologic deficits, and one third have mild residual neurologic deficit or are free from it. The factors predictive of poor stroke prognosis and outcome are: advanced age; male sex; presence of diabetes mellitus, hypertension, or cardiac disease; temperature; dysphagia; incontinence; consciousness disturbance; severe neurologic deficit; cognitive disorders; localization and size of infarction; edema and shift of central structures; biochemical and hematologic disorders, etc.

A fatal outcome of stroke is due to central and peripheral complications. The most common central complications are: cerebral edema, transtentorial herniation, hemorrhagic transformation of ischemia, epileptic seizures, and depression. In stroke patients, death is much more frequently caused by peripheral (systemic) complications such as deep venous thrombosis and pulmonary embolism, bronchopneumonia, urinary infection, septicemia, aspiration, cardiac arrhythmia, myocytolysis, uncontrolled hypotension, and sudden death.

In Europe, the mortality rates for stroke greatly vary. The highest stroke mortality rate of 249 deaths *per* 100,000 inhabitants has been recorded in Bulgaria, and the lowest rate of 27 deaths *per* 100,000 inhabitants in Switzerland. East European countries have a higher total mortality rate, whereas lowest rates have been reported from Scandinavian countries, Switzerland and the Netherlands. Over the last few decades, stroke mortality rates have been dramatically reduced in Japan and Western Europe. In contrast, a constant increase in the stroke mortality rates has been recorded in East European countries, and has been observed to continue in the conditions of transition in these countries. The studies showing secular changes in a disease mortality over years or decades are of special importance.

Neuroepidemiologic studies of stroke have a significant role for correct programming and planning of health care and its specific organization. Also, these studies provide a comprehensive insight into the natural course of the disease, cause of the disease, and allow for the effects of genetically determined and exogenous factors on the occurrence and development of the disease to assess.

*standardized incidence rates*). Međunarodne epidemiološke studije pokazuju da stope incidencije rastu eksponencijalno s dobi, te se kreću između 0,3 promila u trećem i četvrtom desetljeću života, sve do 30 promila u osmom i devetom desetljeću života, što u prosjeku iznosi 1-2 promila. Stope prevalencije MU-a u svijetu variraju između 5 promila i nekoliko postotaka. Procjenjuje se da otprilike jedna trećina oboljelih od moždanog udara umire, druga trećina ima teži, a treća trećina lakši rezidualni neurološki deficit ili je bez deficita. Čimbenici koji predviđaju lošu prognozu i ishod MU-a su: visoka životna dob, muški spol, postojanje dijabetesa, arterijske hipertenzije i srčane bolesti u oboljelih, temperatura, disfagija, inkontinencija, pogoršanje svijesti, težak neurološki deficit, kognitivni poremećaji, lokalizacija i veličina infarkta, edem i pomak središnjih struktura, biokemijski i hematološki poremećaji itd. Smrtni ishod MU-a uzrokuju središnje i periferne komplikacije. Najčešće središnje komplikacije su: cerebralni edem, transtentorialna hernijacija, hemoragijska transformacija ishemije, epileptični napadaji, depresija. Znatno češće smrt bolesnika s MU-om uzrokuju periferne (sistemske) komplikacije: duboka venska tromboza i plućna embolija, bronhopneumonija, urinarni infekt, septikemija, aspiracija, srčana aritmija, miocitoliza, nekontrolirana hipotenzija, nagla smrt. Stope smrtnosti od MU-a u Europi značajno se razlikuju. Najviše stope od 249 umrlih/100.000 stanovnika zabilježene su u Bugarskoj, a najniže od 27/100.000 stanovnika u Švicarskoj. Istočnoeuropske zemlje imaju višu ukupnu smrtnost, dok su najniže stope zabilježene u skandinavskim zemljama, Švicarskoj i Nizozemskoj. Stope smrtnosti dramatično su smanjene tijekom zadnjih nekoliko desetljeća u Japanu i zapadnoeuropskim zemljama. Nasuprot tome, u istočnoeuropskim zemljama u tom razdoblju bilježi se stalan porast stope smrtnosti od MU-a, što se nastavlja i u uvjetima tranzicije ovih zemalja. Od osobitog su značenja studije koje pokazuju sekularne promjene u mortalitetu od neke bolesti kroz dugo razdoblje godina ili desetljeća. Neuroepidemiološke studije MU-a vrlo su važne za ispravno programiranje i planiranje zdravstvene službe i njezine specifične organizacije. Usto, one omogućuju potpunije sagledavanje prirodnog tijeka bolesti, uzroka bolesti, te prosudbu utjecaja genetski određenih i egzogenih čimbenika na pojavu i razvoj bolesti.

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# AKTIVNOSTI ZNANSTVENO-ISTRAŽIVAČKE GRUPE ZA ORGANIZACIJU NEUROLOŠKE SLUŽBE SVJETSKE NEUROLOŠKE FEDERACIJE U LIJEČENJU I PREVENCIJI CEREBROVASKULARNIH BOLESTI

## THE ACTIVITIES OF THE WFN RG ODNs IN THE MANAGEMENT AND PREVENTION OF CEREBROVASCULAR DISEASES

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Since its foundation in 1989, the World Federation of Neurology Research Group on Organization and Delivery of Neurological Services (WFN RG ODNs) has in its center of interest the “mass neurological diseases”, which can be successfully treated and prevented, with clear “cost – benefit” ratios. For this reason, the cerebrovascular diseases (CVD) were in a constant focus of the RG. On several meetings and conferences, factors important for the planning of comprehensive care for CVD were stressed.

Changes in stroke mortality may result from changes in stroke incidence or case fatality. Several studies from developed countries have reported a fall in case fatality, while the decline in the incidence of stroke has stopped

Od svojega osnutka 1989. godine Znanstveno-istraživačka grupa za organizaciju neurološke službe (ZIG) Svjetske neurološke federacije (SNF) stavila si je u središte zanimanja “masovne neurološke bolesti” koje se mogu uspješno liječiti i prevenirati, s pozitivnim odnosom “cijene i korisnosti”. Zbog toga su cerebrovaskularne bolesti (CVB) bile u stalnom žarištu djelovanja ZIG. Na nekoliko sastanaka i konferencija bili su naglašeni čimbenici presudni za planiranje sveobuhvatne brige za prevenciju i liječenje CVB. Promjene u smrtnosti od moždanog udara (MU) mogu biti rezultat promjena u incidenciji MU ili letaliteta oboljelih. U nekoliko studija iz razvijenih zemalja izvještavano je o padu letaliteta oboljelih, dok je smanjivanje in-

and even some increase has become evident. Studies from Eastern Europe have shown an increased incidence, while the trends for case fatality have not been uniform. The social burden of stroke will probably continue to increase beyond 2000 due to the aging of the world population.

A neuroepidemiological approach to the problems encountered in stroke prevention has been accepted by the RG, as proposed by Gorelick. As the proportion of the elderly rises in our populations, understanding of trends in stroke mortality and morbidity is important for planning public health services and measures to control stroke. Stroke is well suited for prevention as it has a high prevalence and social burden of illness, high economic cost, and safe and effective prevention measures capable to prevent stroke, leading to substantial economic savings and reduction in human suffering.

There are two major strategies to prevent stroke: (a) 'mass approach' emphasizes lifestyle modification to achieve modest reductions in the level of a risk factor in all individuals in the population. Examples include proper diet to lower hypertension, cholesterol and fat intake, restriction in heavy alcohol consumption, smoking cessation, and promotion of other healthy lifestyle behaviors in the target population. These are advanced through community-wide health education, legislation and economic measures, as described in Finland; (b) 'high-risk approach' identifies persons in the community with high levels of risk factors. Highly specific medication is required to achieve substantial reductions of the risk factors in an individual patient. The mass and high-risk approaches are considered complementary for prevention.

### Conclusions:

1. Continuous neuroepidemiological studies on regional and local scale are needed in order to obtain better understanding and find the truly represented, locally dominant risk and etiologic factors, determining the genesis and further development of CVD in the investigated population, with due consideration of the great differences in the intrinsic and extrinsic risk factors.

2. Collaborative efforts on national and international levels are needed to find the best possible, most rational, locally applicable strategy in the prevention and early detection of CVD according to the described neuroepidemiological approaches, giving the best cost-effectiveness ratio, considering the different methodologies used in mass approach and high-risk approach.

3. The RG ODNs proposes usage of the relatively inexpensive methods in primary individual screening: clinical neurophysiological (EEG and others), biochemical and

cidencije udara prestalo ili se čak očitovao i određen porast incidencije. Studije iz Istočne Europe pokazale su povećanu incidenciju, dok trendovi letaliteta oboljelih nisu pokazivali ujednačenost. Teret od MU će u godinama iza 2000. vjerojatno i dalje rasti zbog starenja stanovništva. U ZIG je bio prihvaćen neuroepidemiološki pristup u prevenciji MU, što ga je predložio Gorelick. Kako udjel starijih osoba stalno raste, razumijevanje trendova morbiditeta i mortaliteta MU je važno za planiranje službi javnog zdravstva i poduzimanje mjera za kontrolu udara. MU je prikladan za prevenciju budući da ima visoku prevalenciju i predstavlja visok društveni teret i visoku ekonomsku cijenu, a omogućuje sigurne preventivne mjere koje mogu dovesti do značajnih ekonomskih ušteda i smanjenja ljudskih patnji. Dvije su glavne strategije za prevenciju MU: a) "masovni prilaz" (*mass approach*) naglašava promjenu načina života kako bi se postiglo umjereno sniženje razine čimbenika rizika kod svih pojedinaca u populaciji. Primjer uključuje odgovarajuću dijetu za smanjenje visokog tlaka, kolesterola i razine masti u hrani, ograničenje potrošnje teških alkoholnih pića, prestanak pušenja, te promoviranje zdravog načina života u ciljnoj populaciji. Ovi napretci se postižu široko zasnovanim mjerama u zajednici, po uzoru na finsko iskustvo, uz prateće zakonodavne i ekonomske mjere; b) "prilaz bolesnicima visokog rizika" identificira osobe s visokim razinama čimbenika rizika u zajednici. U načelu je ovdje potrebno specifično individualno liječenje za značajnije sniženje postojećih čimbenika rizika u ugroženog bolesnika. Oba prilaza, "masovni" i "visokog rizika", komplementarni su u uspješnoj prevenciji MU.

### Zaključci:

1. ZIG naglašava potrebu stalnih neuroepidemioloških studija na regionalnoj i lokalnoj razini u cilju boljeg razumijevanja i pronalaženja prisutnih i lokalno dominantnih rizičnih i etioloških čimbenika CVB koji određuju genezu i razvoj specifičnih oblika CVB u istraživanoj populaciji. To će omogućiti bolje razumijevanje postojećih velikih razlika u endogenim, ali još više u egzogenim čimbenicima rizika;

2. Suradnja na nacionalnoj i međunarodnoj razini može osigurati pronalaženje najbolje moguće i najracionalnije, lokalno korisne strategije u prevenciji i ranom otkrivanju CVB prema opisanom neuroepidemiološkom načelu koje daje najbolje rezultate u odnosu cijene i korisnosti, a na temeljima našeg razumijevanja različnosti metodologija koje rabimo u "masovnom" i prilazu "visokog rizika";

3. Predlaže se uporaba relativno jeftinih metoda za potrebe primarnog individualnog "probiranja" (*screening*): kliničke neurofiziološke (EEG i druge), biokemijske i neurosonografske metode temeljene na kliničkim i neuroepidemiološkim podacima;



neurosonographic methods, based on clinical analyses and neuroepidemiological data.

4. Specific prevention and therapeutic methods are proposed in order to postpone the development of CVD and stroke to the later phase of human life in a specific community.

5. Organization of modern, scientifically based approaches to the management of 'hyperacute stroke', understanding the pathophysiology of this cerebrovascular catastrophe, e.g., using the best possible, locally available management possibilities of the 'therapeutic window'.

6. Organize the best, locally applicable design in the strategies for the primary and secondary prevention, early diagnosis, best possible management of stroke as well as in rehabilitation and resocialization of stroke patients.

4. Predlaže se primjena specifičnih preventivnih i terapijskih metoda u našoj težnji odlaganja CVB i MU za kasnije razdoblje čovjekova života, kad je i koliko je to moguće u određenoj zajednici;

5. Također se preporuča uporaba modernih, znanstveno potpuno utemeljenih metoda liječenja "hiperakutnog MU", na temelju razumijevanja patofiziologije ove cerebrovaskularne katastrofe, primjenjujući najbolje lokalno primjenjivo liječenje uz uporabu tzv. "terapijskog prozora";

6. Organizirati najbolju lokalno primjenjivu strategiju u primarnoj i sekundarnoj prevenciji, ranoj dijagnozi, najboljem mogućem liječenju, te u rehabilitaciji, neurološkoj restituciji i resocijalizaciji bolesnika nakon doživljenog MU.

## PATHOPHYSIOLOGY OF ATHEROSCLEROSIS AND RISK FACTORS FOR STROKE PATOFIZIOLOGIJA ATEROSKLEROZE I ČIMBENICI RIZIKA ZA NASTANAK MOŽDANOG UDARA

### PATHOPHYSIOLOGY OF ATHEROSCLEROSIS

### PATOFIZIOLOGIJA ATEROSKLEROZE

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Although many factors are involved in the genesis of atherosclerosis, hypercholesterolemia, i.e. increased LDL concentration in blood is considered the major risk factor for its development. Other highly relevant risk factors are hypertension, type II diabetes mellitus, obesity, cigarette smoking, inadequate physical activity, stress, etc.

Nowadays, the process of atherosclerosis is believed to be initiated by the activation or lesion of endothelial cells, whereby free oxygen radicals play a central role. The risk factors, especially hypercholesterolemia and arterial hypertension, cause so-called oxidative stress in endothelial cells. In patients with type II diabetes mellitus, the same effect is exerted by stable glycosylated protein. Also, free oxygen radicals are taken directly into the body with cigarette smoke.

Free oxygen radicals act as messenger molecules and stimulate the expression of adhesion molecules by the transcription system activation. An important transcription system thus activated is the NF- $\kappa$ B. The occurrence of an ever increasing number of adhesion molecules on endothelial cell membranes leads to monocyte adherence to the arterial endothelium, with simultaneous LDL penetration through the intact endothelium. LDL are then oxidized in the subendothelial space under the action of endothelial cell lipoperoxidase and free oxygen radicals formed in

Iako u nastanku ateroskleroze sudjeluje mnoštvo čimbenika, hiperkolesterolemija, odnosno povišena koncentracija LDL-a u krvi smatra se najvažnijim čimbenikom rizika u njezinom nastanku. Ostali važni čimbenici su hipertenzija, šećerna bolest tipa II., pretilost, pušenje, smanjena tjelesna aktivnost, stres i drugi. Danas se smatra da proces ateroskleroze započinje aktiviranjem ili oštećenjem endotelnih stanica, pri čemu slobodni radikali kisika imaju središnju ulogu. Čimbenici rizika, a posebno hiperkolesterolemija i arterijska hipertenzija, u endotelnim stanicama uzrokuju tzv. oksidativni stres. U oboljelih od tipa II. šećerne bolesti stabilno glikozilirane bjelanjčevine djeluju na isti način. S cigaretnim dimom se izravno u organizam unose slobodni radikali kisika.

Slobodni radikali kisika djeluju kao vjesničke molekule i potiču aktiviranjem transkripcijskih sustava izražaj adhezijskih molekula. Važan transkripcijski sustav koji se aktivira je NF- $\kappa$ B.

Pojava sve većega broja adhezijskih molekula na membranama endotelnih stanica dovodi do prijanjanja monocita uz endotel arterija uz istodobni prodor LDL-a kroz intaktan endotel te se isti u subendotelnom prostoru oksidira pod djelovanjem lipoperoxidaze endotelnih stanica i slobodnih radikala kisika nastalih u istim stanicama, ali i slobodnih radikala kisika iz makrofaga i glatkih mišićnih sta-

these cells as well as of free oxygen radicals from the macrophages and smooth muscle cells. The oxidized LDL have different properties than LDL. Oxidized LDL are chemotactic for monocytes, cytotoxic, and immunogenic. Oxidized LDL enter the cells *via* special scavenger receptors located on macrophage membranes. Oxidized LDL stimulate endothelial cells to secrete chemokines and cytokines, which in turn stimulate the process of monocyte migration to the subendothelial space and their differentiation to macrophages. Because of strong chemotaxis, the oxidized LDL attract macrophages in the subendothelial space. Oxidized LDL enter the macrophages *via* scavenger receptors. These scavenging receptors possess no down-regulation ability, thus a large amount of oxidized LDL enter the macrophages, and they eventually transform into foam cells. The entry of oxidized LDL stimulates the macrophages to secrete a number of active substances such as cytokines, PDGF, interleukin 1, TNF, alfa and beta transforming growth factors, etc. T lymphocytes, being attracted to the subendothelial space, release cytokines. Cytokines stimulate endothelial cells to secrete adhesion molecules on their membranes, which in turn enable adhesion of an ever growing number of monocytes to the vascular wall, and stimulate proliferation of the media smooth muscle cells. Oxidized LDL damage the blood vessel endothelium by their pronounced cytotoxic effect. Endothelial lesion may also be induced by the mechanical action of elevated blood pressure or recurrent arterial spasm. In the endothelium thus damaged, the synthesis of the platelet aggregation inhibitor prostacyclin (PGI<sub>2</sub>) is diminished, with simultaneously increased synthesis of the platelet aggregation stimulator thromboxane (TxA<sub>2</sub>); both of these processes favor the occurrence of microthrombi. The platelet growth factor is released from the platelets and stimulates, along with LDL and some hormones (primarily insulin), the smooth muscle cell migration from the media to the intima, and their proliferation at the site of lesion. This effect of LDL is inhibited by HDL, and it is one of the HDL antiatherosclerotic actions. The platelet growth factor released from the platelets also stimulates the synthesis of scavenger receptors in smooth muscle cells, so that they assume a foam cell appearance. This initial stage of the disorder, when lipids are mostly found within the foam cells, is called fatty streak that may disappear unless the mechanisms of excess cellular cholesterol elimination are impaired. In case of permanently elevated LDL concentrations and recurrent lesions, the atherosclerotic process will progress, whereby foam cells disintegrate, thereby releasing the substances that stimulate smooth muscle cell and fibroblast proliferation. The lipids in the macrophages undergo oxidation to toxic rad-

nica. Oksidirani LDL ima drukčija svojstva od LDL-a. Oksidirani LDL je kemotaksičan za monocite, citotoksičan je i imunogen je. Oksidirani LDL u stanice ulazi posredstvom posebnih receptora-čistača koji se nalaze na membranama makrofaga. Oksidirani LDL potiče endotelne stanice na lučenje kemokina i citokina, a oni stimuliraju proces seljenja monocita u subendotelni prostor i njihovu diferencijaciju u makrofage. Zbog jake kemotaksije oksidirani LDL privlači makrofage u subendotelnom prostoru. U makrofage ulaze oksidirani LDL-i posredstvom receptora-čistača. Receptori čistači nemaju sposobnost regulacijskoga sniženja, tako da u makrofage ulazi velika količina oksidiranih LDL-a i oni se na kraju pretvaraju u pjenaste stanice. Ula-zak oksidiranih LDL-a u makrofag aktivira makrofage na lučenje mnogih aktivnih tvari kao što su citokini: PDGF, interleukin 1, TNF, transformirajući čimbenik rasta alfa i beta i dr. T limfociti koji se nalaze privučeni u subendotelni prostor luče citokine. Citokini potiču endotelne stanice da na svoje membrane izluče adhezijske molekule koje pak omogućuju prijanjanje sve većega broja monocita uza stijenu krvne žile uz poticanje proliferacije glatkih mišićnih stanica medije. Izraženim citotoksičnim učinkom oksidirani LDL oštećuje endotel krvne žile. Endotel se može oštetiti i uslijed mehaničkoga djelovanja povišenoga krvnoga tlaka, dužega ili opetovanoga spazma arterija. U tako oštećenom endotelu smanjena je sinteza inhibitora agregacije trombocita prostaciklina (PGI<sub>2</sub>) uz istodobno povećanu sintezu pojačivača agregacije trombocita tromboksana (TxA<sub>2</sub>), a oba procesa pogoduju nastanku mikrotromba. Iz trombocita se oslobađa trombocitni čimbenik rasta koji zajedno s LDL-om i nekim hormonima (ponajprije inzulinom) potiče putovanje glatkih mišićnih stanica iz medije u intimu i njihovo umnažanje na mjestu lezije. HDL koči taj učinak LDL-a i to je jedno od njegovih protuaterosklerotskih djelovanja. Trombocitni čimbenik rasta oslobođen iz trombocita potiče i sintezu receptora čistača u mišićnim stanicama, tako da i one poprimaju izgled pjenastih stanica. Ovaj početni stadij poremećaja kada lipide nalazimo pretežito unutar pjenastih stanica zovemo masnom prugom koja može i nestati ako nisu oštećeni mehanizmi uklanjanja suvišnog kolesterola u stanicama. U slučaju pak trajno povišenih koncentracija LDL-a i ponavljano oštećenja proces ateroskleroze napreduje, pri čemu pjenaste stanice propadaju, iz njih se oslobađaju tvari koje potiču umnažanje glatkih mišićnih stanica i fibroblasta. Dolazi do oksidacije lipida u makrofagima u toksične radikale (prevladavaju peroksidi) koji razarajući okolne stanice pridonose širenju aterosklerotskog oštećenja. Zbog nakupljanja sve veće količine kolesterola iz LDL-a stimulira se sinteza kolagena, elastina i mukopolisaharida u glatkim mišićnim stanicama te njihovo pojačano odlaganje tvori

icals (peroxides prevail), which destroy the surrounding cells and thus contribute to propagation of the atherosclerotic lesion. The accumulation of ever more cholesterol from LDL stimulates the synthesis of collagen, elastin and mucopolysaccharides in smooth muscle cells, and their enhanced deposition leads to the formation of atheroma. The atheroma leads to intimal thickening at the site of endothelial lesion, thus modifying the blood flow and causing further endothelial damage and lesion propagation. Atherosclerosis narrows the lumen of the vessel, leading to tissue hypoxia. The loss of vascular elasticity leads to blood pressure elevation, increasing the risk of vascular wall rupture and hemorrhage into the tissue.

aterom. Aterom uzrokuje zadebljanje intime na mjestu oštećenja endotela, čime se tijekom krvi mijenja, što pak uzrokuje daljnja oštećenja endotela i širenje lezije. Ateroskleroza sužava promjer žile, što vodi ka tkivnoj hipoksiji. Gubitak elasticiteta krvne čile dovodi do povećanja krvnoga tlaka, čime se povećava rizik od puknuća stijenke i krvarenja u tkivo.

## ATHEROSCLEROSIS AND INFLAMMATION

### ATEROSKLEROZA I UPALA

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Atherosclerosis underlies a majority of stroke cases. Atherosclerosis has classically been described as a progressive disease characterized by the deposition of lipids, fibrous material and calcium in the arterial wall. Recent concepts point to the central role of inflammatory process in the development of both atheroma and thrombus on the atheroma. Inflammatory process is present in the earliest as well as advanced atherosclerotic lesions. Besides the action of other known risk factors for the onset and progression of atherosclerosis, it is ever more evident that inflammation plays a major role in atherogenesis.

In the very beginning of atherogenesis, the initial lesion of the arterial endothelium occurs. The endothelial lesion may be caused by the inflammatory process. The endothelial cells involved by the lesion have a diminished vasodilatory function, and an array of proinflammatory functions are activated on the damaged endothelium, such as expression of adhesion molecules (VCAM and ICAM) on the endoluminal wall of the endothelium, and cytokine and complement release, causing monocyte adhesion

U podlozi većine moždanih udara nalazi se ateroskleroza. Ateroskleroza se klasično opisivala kao progresivna bolest obilježena nakupljanjem lipida, fibroznog materijala i kalcija u stijenci arterija. Novije spoznaje ukazuju na središnje značenje upalnog procesa kako u nastanku ateroma tako i u nastanku tromba na ateromu. Upalni proces prisutan je u najranijim aterosklerotskim lezijama kao i u uznapredovalim lezijama. Uz djelovanje ostalih poznatih čimbenika rizika za nastanak i progresiju ateroskleroze postaje sve jasnije da upala igra vrlo značajna ulogu u aterogenezi.

U samom početku aterogeneze dolazi do početnog oštećenja endotela arterija. Moguće je da upalni proces uzrokuje oštećenje endotela. Oštećene stanice endotela imaju smanjenu vazodilacijsku funkciju, a na oštećenom endotelu aktivira se cijeli spektar proupalnih funkcija: dolazi do ekspresije adhezijskih molekula (VCAM i ICAM) na endoluminalnoj stijenci endotela, oslobađaju se citokini i komplement, što uzrokuje adheziju monocita na leziju i ulazak monocita u subendotelni prostor kroz oštećeni

to the lesion and monocyte migration to the subendothelial space through damaged endothelium. In the subendothelial space, the inflammatory process continues, thus being responsible for the most significant events in atherosclerosis, i.e. oxidation of LDL particles; monocyte recruitment and transformation to macrophages; formation of foam cells and lipid deposits; platelet activation; smooth muscle cell migration and proliferation; and synthesis of extracellular matrix and connective tissue.

In addition to the genesis of atherosclerotic lesions, inflammation has a significant role also in the progression of these lesions. It appears that rupture of the plaque cap and release of the plaque content into the circulation is the most important factor that leads to the progression of atherosclerosis. Plaque composition is of utmost importance for the occurrence of plaque rupture, consequential plaque progression, and development of clinically significant thrombotic complications. Soft plaques have large lipid nuclei, abundance of inflammatory cells (mostly macrophages and T lymphocytes), rare smooth muscle cells, and thin cap composed of fragmented collagen. Solid, fibrous plaques have small lipid nuclei, rare inflammatory cells, abundant smooth muscle cells, and thick cap composed of type I and III collagen, elastin and proteoglycans synthesized by smooth muscle cells. Soft plaques are much more susceptible to rupture than fibrous plaques. During the inflammatory process, the enzyme myeloperoxidase, elastolytic cathepsins and metalloproteases are being released, leading to decomposition and structural weakening of the plaque cap. In addition, T lymphocytes produce gamma interferon, which significantly reduces the synthesis of collagen. Both of these processes can result in plaque rupture, thrombus formation on the ruptured plaque, and consequential clinical complications.

Thus, it is obvious that inflammatory process plays a major role in both the occurrence and progression of atherosclerotic lesions. Inflammatory process can be 'sterile', with *Chlamydia pneumoniae*, *Haemophilus influenzae*, *Mycoplasma pneumoniae*, *Helicobacter pylori*, *cytomegalovirus*, *herpes simplex virus*, and *Epstein-Barr virus* reported as candidate agents. These microorganisms have been found in various atherosclerotic lesions as well as in patients with clinical complications of atherosclerosis (myocardial infarction, stroke), supporting the role of these pathogens in the genesis of inflammation that can lead to the onset and progression of atherosclerotic lesions. The action of antibiotics, mostly macrolides, in the prevention of onset and progression of atherosclerotic lesions has been investigated, however, no results confirming the efficacy of antibiotics in the prevention of atherosclerosis have been reported to date.

endotel. U subendotelnom prostoru nastavlja se upalni proces koji je odgovoran za najznačajnije događaje u aterogenezi: oksidaciju LDL čestica, regrutiranje monocita i transformaciju u makrofage, nastanak pjenušavih stanica i depozita lipida, aktiviranje trombocita, migraciju i proliferaciju glatkih mišićnih stanica, sintezu ekstracelularnog matriksa i vezivnog tkiva. Uz onu u nastanku ranih aterosklerotskih lezija, upala ima značajnu ulogu i u progresiji aterosklerotskih lezija. Izgleda da je najznačajniji čimbenik koji dovodi do progresije ruptura kape plaka i izlaganje sadržaja plaka krvnoj struji, što dovodi do nastanka tromba na plaku. U nastanku rupture plaka, posljedične progresije plaka i pojavljivanju klinički značajnih trombotičkih komplikacija vrlo je važna građa plaka. Meki plakovi imaju veliku lipidnu jezgru, mnoštvo upalnih stanica (pretežito makrofaga i T limfocita), rijetke glatke mišićne stanice i tanku kapu građenu od fragmentiranog kolagena. Tvrdi, fibrozni plakovi imaju malu lipidnu jezgru, rijetke upalne stanice, mnoštvo glatkih mišićnih stanica i debelu kapu građenu od kolagena tipa I. i III., elastina i proteoglikana koje sintetiziraju glatke mišićne stanice. Meki plakovi mnogo su skloniji rupturi od fibroznih. Tijekom upalnog procesa oslobađaju se enzimi mijeloperoksidaze, elastolitički katepsini i metaloproteaze koje razgrađuju makromolekule kape plaka, što uzrokuje slabljenje strukture kape plaka. Uz to T limfociti proizvode gama interferon koji značajno smanjuje sintezu kolagena. Oba procesa mogu dovesti do rupture plaka, nastanka tromba na rupturiranom plaku i posljedičnih kliničkih komplikacija. Vidljivo je da upalni proces ima značajnu ulogu kako u nastanku tako i u progresiji aterosklerotskih lezija. Upalni proces može biti «sterilan», a od mogućih uzročnika spominju se *Chlamydia pneumoniae*, *Haemophilus influenzae*, *Mycoplasma pneumoniae*, *Helicobacter pylori*, *cytomegalovirus*, *herpes simplex virus*, *Epstein-Barrov virus*. Ovi mikroorganizmi nađeni su u raznim aterosklerotskim lezijama, kao i u bolesnika s kliničkim komplikacijama ateroskleroze (infarkt miokarda, moždani udar), što govori u prilog uloge navedenih patogena u nastanku upale koja može dovesti do nastanka i progresije aterosklerotskih lezija. Ispituje se djelovanje antibiotika, uglavnom makrolida, u prevenciji nastanka i progresije aterosklerotskih lezija, no zasada nisu objavljeni rezultati koji bi potvrdili djelotvornost primjene antibiotika u prevenciji ateroskleroze.

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## ARTERIAL HYPERTENSION AND ATRIAL FIBRILLATION – RISK FACTORS FOR STROKE

### ARTERIJSKA HIPERTENZIJA I ATRIJSKA FIBRILACIJA: ČIMBENICI RIZIKA MOŽDANOG UDARA

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Cardiovascular disease is the leading cause of death in adults aged  $\geq 30$  years in industrialized countries. Coronary disease is the major 'culprit', followed by stroke. Atherosclerosis underlies the anatomic and pathologic background of these entities. In Croatia, cardiovascular disease is the cause of death in 53% of cases, showing an increasing tendency and shift towards younger age groups.

Hypertension is the major modifiable risk factor for stroke and intracranial hemorrhage. The incidence of stroke rises proportionally with systolic and diastolic blood pressure. Blood pressure, especially systolic blood pressure, rises with age. Isolated systolic hypertension (systolic blood pressure  $> 160$  mm Hg, and diastolic blood pressure  $< 90$  mm Hg) is an important risk factor for stroke in the elderly. Intensive blood pressure control (BP  $< 140/90$ , and  $< 130/80$  in diabetics) has reduced stroke morbidity and mortality by 40%. The HOPE and PROGRESS studies have shown the prevention of stroke to exceed the one expected from blood pressure reduction alone. In spite of education, a high proportion of the population have non-diagnosed or poorly treated hypertension. The recommendations include regular blood pressure measurement in adults, i.e. at least every two years, and intensive treatment in line with the recommendations.

Kardiovaskularna bolest je najčešći uzrok smrti u razvijenim zemljama među odraslima starijim 30 ili više godina. Koronarna bolest je glavni krivac nakon kojega slijedi moždani udar. Anatomska i patološka osnova ovih entiteta je ateroskleroza. U Hrvatskoj je kardiovaskularna bolest uzrok smrti u 53% slučajeva, pokazuje trend porasta i pomicanje prema mlađoj dobnoj skupini. Hipertenzija je glavni čimbenik rizika za moždani infarkt i intrakranijsko krvarenje na koji je moguće utjecati. Incidencija moždanog udara raste proporcionalno sa sistoličkim i dijastoličkim krvnim tlakom. Krvni tlak, naročito sistolički, raste s dobi. Izolirana sistolička hipertenzija (sistolički krvni tlak  $> 160$  mm Hg, a dijastolički  $< 90$  mm Hg) je važan čimbenik rizika moždanog udara u starijih osoba. Intenzivna kontrola krvnog tlaka (RR  $< 140/90$ , dijabetičari RR  $< 130/80$ ) smanjila je morbiditet i mortalitet od moždanog udara za 40%. Studije HOPE i PROGRESS pokazale su prevenciju moždanog udara veću nego što se očekuje sniženjem krvnog tlaka. Usprkos naporu u edukaciji, značajan postotak populacije ima nedijagnosticiranu ili loše liječenu hipertenziju. Preporuka je redovno mjerenje krvnog tlaka u odraslih, najmanje svake dvije godine, i intenzivno liječenje prema preporukama. Atrijska fibrilacija je česta aritmija i važan čimbenik rizika moždanog udara. Godišnji rizik moždanog

Atrial fibrillation is a common arrhythmia and an important risk factor for stroke. In patients with nonvalvular atrial fibrillation, the annual risk of stroke is 3% - 5%. Atrial fibrillation is responsible for 15% - 20% of ischemic stroke cases. The risk factors for stroke in patients with atrial fibrillation include a history of stroke or transient ischemic attack, hypertension, history of hypertension, depressed left ventricular function, cardiomegaly, left ventricular hypertrophy, diabetes mellitus, left atrial enlargement > 50 mm, transesophageal echocardiography finding of a thrombus in the left atrium, age, and coronary disease. Longterm oral anticoagulant therapy reduced the risk of stroke by 68% in risk patients with atrial fibrillation. However, anticoagulant therapy has generally been inadequately prescribed and poorly conducted in patients with atrial fibrillation. The incidence of stroke in the elderly can be reduced by a wider and more appropriate use of a combination of aspirin and warfarin.

udara u bolesnika s nevalvularnom fibrilacijom atrija je 3% do 5%. Atrijska fibrilacija odgovorna je za 15%-20% cerebrovaskularnih događaja ishemijskog uzroka. Čimbenici rizika moždanog udara su preboljeli moždani udari ili tranzitoma ishemijska ataka (TIA) u anamnezi, hipertenzija i hipertenzija u anamnezi, smanjena funkcija lijevog ventrikula, kardiomegalija, hipertrofija lijevog ventrikula, dijabetes, uvećan lijevi atrij > 50 mm, transezofagealni ehokardiografski nalaz tromba u lijevoj atriju, dob i koronarna bolest. Dugotrajna oralna antikoagulantna terapija rizičnih bolesnika s atrijskom fibrilacijom smanjila je rizik moždanog udara za 68%. Međutim, antikoagulantna terapija se slabo primjenjuje i loše vodi u rizičnih bolesnika s atrijskom fibrilacijom. Šira i prikladnija upotreba kombinacije aspirina i varfarina smanjiti će incidenciju moždanog udara u starih osoba.

## STROKE IN DIABETIC PATIENTS

### MOŽDANI UDAR U OSOBA SA ŠEĆERNOM BOLEŠĆU

Ante Ivandić

Not received

Nije primljeno

## CIGARETTE SMOKING AS A RISK FACTOR FOR STROKE

### PUŠENJE KAO ČIMBENIK RIZIKA ZA MOŽDANI UDAR

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Among numerous risk factors that are responsible for the onset and development of stroke, cigarette smoking is emphasized as a factor that simultaneously affects the

Među brojnim rizičnim čimbenicima odgovornim za razvoj i nastanak moždanog udara pušenje se ističe kao čimbenik koji istodobno na različite načine ugrožava funkcion-

circulatory system function in a number of ways. By either active or passive cigarette smoking, several thousands of various chemical substances are taken to the body. Many studies have investigated the mechanisms of action of particular tobacco smoke components on the vascular system and other organ systems in the body, whereas their interactions as well as interferences with various drugs still remain partially obscure.

Depending on the number of cigarettes, smokers have been found to have significantly higher levels of total cholesterol, triglycerides, very low density lipoprotein (VLDL) and low density lipoprotein (LDL), and lower levels of high density lipoprotein (HDL) and apolipoprotein A1, known for their angioprotective action. In smokers, due to impaired lipolysis, the intake of fatty meal is not followed by a HDL increase, which is normally observed in nonsmokers. This phenomenon has been explained by the fact that nicotine stimulates the release of adrenaline, followed by an increase in the concentration of free fatty acids (FFA), which stimulate hepatic secretion of VLDL. The concentration of HDL changes inversely to the concentration of VLDL. In addition, an elevated concentration of thromboxane A2 and increased platelet reactivity have been recorded in smokers. Smokers also have elevated levels of factor VII and fibrinogen. The release of prostacycline and EDR factor, which regulate basal vascular tonus, is also impaired in longterm smokers. Some studies have suggested the possible endothelial cell damage by carbon monoxide contained in tobacco smoke, thus increasing the vascular wall permeability and enabling massive lipid infiltration. In addition to these mechanisms of action, cigarette smoking induces a number of other processes that contribute to atherogenesis.

The specific feature of cigarette smoking is that a heterogeneous mixture of more than 4000 different chemical compounds are usually taken to the body on 20 or more occasions daily over a long period of time. The repetitive sympathetic stimulation and vasoconstrictive action of nicotine, along with a decreased blood oxygen level, because hemoglobin has been in part transformed to the physiologically inactive carboxyhemoglobin, contribute significantly to the development of atherogenesis.

From the pharmacological point of view, nicotine, an alkaloid by its chemical composition, is a tobacco constituent with the most potent action. In addition to aggravating the circulatory system function, nicotine is extremely addictive and is considered responsible for the development of metabolic dependence. Results of epidemiologic studies suggest that a small percentage, not more than 5%, of young people who start smoking remain on only several cigarettes a day, whereas all others gradually develop tolerance and become dependent.

Iranje cirkulacijskog sustava. Aktivnim i pasivnim pušenjem u tijelo se unosi nekoliko tisuća kemijskih sastojaka. Provedeno je niz istraživanja o mehanizmima djelovanja pojedinih komponenata duhanskog dima na vaskularni sustav i druge organske sustave u tijelu, dok se o njihovim međusobnim interakcijama, kao i interferiranju s uzimanjem različitih lijekova još uvijek nedovoljno zna.

Kod pušača je nađeno da ovisno o količini popušenih cigareta imaju značajno višu razinu ukupnog kolesterola, triglicerida, lipoproteina vrlo niske gustoće (VLDL), lipoproteina niske gustoće (LDL) te nižu razinu lipoproteina visoke gustoće (HDL) i apolipoproteina A1, koji imaju angioprotektivno djelovanje. Zbog poremećene lipolize kod pušača nakon što su konzumirali masni obrok ne dolazi do povišenja HDL-a, što se normalno uočava kod nepušača. Ova se pojava objašnjava time što nikotin potiče oslobađanje adrenalina, povećava se koncentracija slobodnih masnih kiselina (FFA) koje potiču jetreno lučenje VLDL-a. Koncentracija HDL-a se mijenja obrnuto s koncentracijom VLDL-a. Uz to, kod pušača je zabilježena i povišena koncentracija tromboksana A2 te povećana reaktivnost trombocita. Pušači također imaju povišenu razinu faktora VII. i fibrinogena. Oslobađanje prostaciklina i faktora EDR koji reguliraju bazalni tonus krvnih žila također je kod dugogodišnjih pušača poremećeno. Postoje istraživanja koja upućuju na mogućnost oštećenja endotelnih stanica ugljik monoksidom što ga sadrži duhanski dim, zbog čega se povećava propusnost stijenke i omogućuje veće infiltriranje lipida. Uz navedene mehanizme djelovanja pušenje izaziva i niz drugih procesa koji doprinose aterogenezi. Specifičnost pušenja je u tome što pušači heterogenu smjesu s preko četiri tisuće različitih kemijskih spojeva najčešće unose u tijelo dvadesetak i više puta na dan, i to kroz dugo razdoblje. Opetovana simpatička stimulacija i vazokonstriktorsko djelovanje nikotina, uza smanjenu razinu kisika u krvi, s obzirom na to da je dio hemoglobina pretvoren u fiziološki neaktivan karboksihemoglobin, značajno doprinose aterogenezi. S farmakološkog stajališta, nikotin, po svom kemijskom sastavu alkaloid, sastojak je duhanskog dima s najsnažnijim djelovanjem. Nikotin je, uz to što ugrožava funkcioniranje cirkulacijskog sustava, izrazito adiktivan i smatra se odgovornim za razvoj metabolične ovisnosti.

Rezultati epidemioloških istraživanja upućuju na to da mali postotak mladih koji počnu pušiti, tek oko pet posto, ostaje na nekoliko cigareta na dan, dok se kod ostalih postupno razvija tolerancija i postaju ovisni. Uzimajući u obzir činjenicu da je pušenje pandemijski prošireno, da broj pušača unatoč svim dokazima o štetnosti pušenja za zdravlje u mnogim zemljama i dalje raste, naročito među mladima, može se u budućnosti, ako se ovaj trend ne promijeni,



Considering the fact that cigarette smoking shows a pandemic spread all over the world, and that the number of smokers still is on an increase in many countries, especially among the young, in spite of all evidence for the detrimental effects of cigarette smoking, an ever rising rate of malignant and circulation diseases that are directly associated with tobacco smoking should be expected in the future, may this unfavorable trend fail to change.

The relative risk of subarachnoid hemorrhage in men, longterm heavy smokers (those smoking >20 cigarettes a day), and in women smokers is 7.3 as compared with the men and women who have never smoked cigarettes. The risk of ischemic stroke is 2.7 in heavy smokers and 2.2 in those smoking <20 cigarettes a day, as compared with nonsmokers. The risk decreases with quitting cigarette smoking.

In the world, it is estimated that every ten seconds one person dies from smoking. Stroke occupies a high place on the scale of morbidity and mortality in both industrialized countries and Croatia. In Croatia, unfortunately, smoking is still one of the major public health problems considering the high proportion of smokers, especially among women and young population. The activities taken in the field of smoking prevention and treatment of smokers are also expected to contribute to the reduction of the prevalence of stroke. The risk of cigarette smoking is still underestimated in the public. The children and adolescents are frequently exposed to direct and indirect pressures to light a cigarette. Both passive and active smoking remains a great problem despite the legal provisions that should help that as much space as possible be freed from cigarette smoke.

Smokers are mostly multiple patients. They more frequently suffer from chronic diseases that require longterm treatment, more frequently require hospitalization, are on sick-leave, become disabled, and die prematurely. There is no healthy level of cigarette smoking.

On the other hand, quitting smoking is accompanied by numerous advantages – physical, emotional, social and economic. Among the advantages of quitting smoking, the reduction in the risk of stroke certainly is one of the most important, as it is known that one third of stroke patients die, one third have to live with minor or major disability, and only one third recover.

očekivati još više malignih i cirkulacijskih bolesti koje su izravno vezane uz pušenje duhana. Relativan rizik od nastanka subarahnoidne hemoragije kod muškaraca, dugogodišnjih teških pušača (oni koji puše više od dvadeset cigareta na dan) i žena pušačica je 7,3 u usporedbi s muškarcima koji nisu nikada pušili i ženama nepušačicama. Rizik od ishemijskog moždanog udara je kod teških pušača 2,7, a kod pušača koji puše manje od dvadeset cigareta na dan 2,2 u odnosu na nepušače. Prestankom pušenja taj se rizik smanjuje. Na razini svijeta računa se da svakih deset sekunda netko umire kao žrtva pušenja. Moždani udar se nalazi visoko na ljestvici mortaliteta i morbiditeta kako u razvijenim zemljama tako i u Hrvatskoj. Pušenje je u Hrvatskoj još uvijek, nažalost, jedan od najvećih javno zdravstvenih problema s obzirom na velik broj pušača, poglavito među ženama i među mladima. Za očekivati je da aktivnosti na području prevencije pušenja i liječenja pušača doprinesu i smanjenju pojavnosti moždanog udara. Rizik pušenja se u javnosti još uvijek podcjenjuje. Djeca i mladi su često izloženi neizravnim i izravnim pritiscima da zapale cigaretu. Pasivno ili prisilno pušenje je još uvijek velik problem unatoč pozitivnim zakonskim propisima koji bi trebali pomoći da što više prostora bude oslobođeno duhanskog dima. Pušači su najčešće višestruki bolesnici. Češće oboljevaju od kroničnih bolesti koje zahtijevaju dugotrajno liječenje, češće borave u bolnici, izostaju s posla, postaju invalidi i prije vremena umiru. Ne postoji zdrava razina pušenja duhana.

Prestanak pušenja, s druge strane, donosi niz prednosti – tjelesnih, emocionalnih, društvenih i gospodarskih. Među prednostima prestanka pušenja smanjenje rizika nastanka moždanog udara je svakako jedna od vrlo značajnih prednosti, s obzirom na to da jedna trećina oboljelih od moždanog udara umire, trećina ostaje živjeti s manjom ili većom invalidnošću, a samo trećina se oporavlja.

## STRES I MOŽDANI UDAR

## STRESS AND STROKE

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Today, most people are permanently exposed to chronic stress due to the ever faster living imposed by the modern lifestyle. In Croatia, even greater proportion of the population are exposed to stress due to the consequences of recent war actions. Although stress certainly is one of the risk factors for the development of cerebrovascular diseases, there are many doubts about the exact definition of the stress concept, and especially of the way of measuring stress severity. A Canadian physician H. Selye was the first to define stress as spiritual or physical overloading of the body by exhaustion. The stress and stressors that provoke stress are divided into acute and longlasting or chronic ones, however, the latter is primarily considered as a risk factor for stroke. Various neurobiological changes in the body induced by stress are well known, e.g., activation of the neurohumoral hypothalamo-pituitary-adrenal axis with consequential production of the stress hormone cortisol. Besides this, stress activates the production of the neurotransmitters adrenaline and noradrenaline, and stimulates activation of the renin-angiotensin system, which in turn results in an enhanced production of angiotensin II, which ultimately precipitates the development of atherosclerosis. In patients with chronic posttraumatic stress disorder (PTSP), prolonged production of cortisol, adrenaline and noradrenaline due to dysfunction of positive feedback mechanism has been demonstrated, which resulted in the vasospasm of the circle of Willis vessels in as many as 62% of patients in some studies. As a higher prevalence of other risk factors has also been recorded in PTSP patients, it suggests that these patients are at a higher risk of stroke. Today it is known that chronic stress also has an immunosuppressive action, and leads to granulocyte, and T and B lymphocyte count decrease, and thus to native and cellular immunity impairment, which then contributes to the morbidity and mortality increase. Prolonged stress also stimulates the development of arterial hypertension, which is the major risk factor for stroke. There are a number of studies pointing to the role of stress as a risk factor for stroke. War is definitely one of the strongest stressors,

U današnjem modernom svijetu je praktično većina ljudi zbog samog ubrzanog načina života pod stalnim utjecajem kroničnog stresa, a u našoj je zemlji broj ljudi pod stresom još i veći zbog posljedica nedavno završenog rata. Iako je stres nedvojbeno jedan od čimbenika rizika za razvoj cerebrovaskularne bolesti, postoji niz dvojbi o točnom definiranju pojma stresa te osobito o načinima mjerenja "jačine" stresa. Kanadanin H. Selye je prvi liječnik koji je stres definirao kao duševno ili tjelesno preopterećenje organizma iscrpljenošću. Sam stres kao i stresori koji ga izazivaju dijele se na akutne i dugotrajne ili kronične, ali se kao na čimbenik rizika za moždani udar prvenstveno misli na dugotrajni stres. Poznate su razne neurobiološke promjene u organizmu pod utjecajem stresa. Tako, primjerice, stres aktivira neurohumoralni hipotalamo-hipofizno-adrenalni sustav s posljedičnim stvaranjem stres hormona kortizola. Uz to, stres aktivira stvaranje neurotransmitera adrenalina i noradrenalina, te potiče aktiviranje renin-angiotenzinskog sustava, što rezultira povećanom proizvodnjom angiotenzina II., što pak u konačnici ubrzava razvoj ateroskleroze. Kod bolesnika s kroničnim posttraumatskim stresnim poremećajem (PTSP) dokazana je produžena proizvodnja kortizola, adrenalina i noradrenalina, i to zbog nefunkcioniranja mehanizma pozitivne povratne sprege, što je u nekim radovima rezultiralo vazospazmom krvnih žila Willisova kruga kod čak 62% ovih bolesnika. Kako je kod bolesnika koji boluju od PTSP-a dokazana povećana učestalost i drugih čimbenika rizika, to upućuje na zaključak da bolesnici koji boluju od ove bolesti imaju povećan rizik za nastanak moždanog udara. Danas se zna kako kronični stres ima i imunosupresivno djelovanje, te da dovodi do pada broja granulocita, T i B limfocita i tako oslabljuje urođenu i staničnu imunost, što doprinosi povećanju morbiditeta i mortaliteta.

Dugotrajan stres također potiče razvoj arterijske hipertenzije koja je sama po sebi najznačajniji čimbenik rizika za nastanak moždanog udara. Postoji niz radova koji na neizravan način pokazuju značenje stresa kao čimbenika rizika za razvoj moždanog udara. Rat je nedvojbeno jedan od najjačih stresora, što je pokazano u radovima koji su

as shown in the studies demonstrating a significantly greater number of patients with intracerebral hemorrhage and subarachnoid hemorrhage in the Osijek area during the war as compared with the peacetime period. A significant increase in the incidence of stroke, especially of hemorrhagic type of stroke, was also recorded in Sarajevo during the war as compared with the peacetime period. Studies analyzing the effect of prolonged stress on the risk factors for cerebrovascular disease have shown a statistically significantly higher proportion of patients with arterial hypertension, hyperlipidemia and obesity in the group of war sufferers-refugees than in the control group of subjects, thus additionally pointing to stress acting as both a risk factor by itself and stimulating the development of other risk factors for stroke. Other studies have demonstrated an increased proportion of stroke patients in the group of refugees as compared with the general population. Accordingly, the present knowledge about stress indicates that prolonged stress is definitely one of the risk factors for stroke, especially for hemorrhagic stroke, and can also additionally increase the prevalence of other risk factors for the development of cerebrovascular disease.

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## PREVENTION OF STROKE PREVENCIJA MOŽDANOG UDARA

### APPROACHES IN THE PREVENTION OF STROKE

### PRISTUPI U PREVENCIJI MOŽDANOG UDARA

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Both Croatian and Anglo-Saxon authors (Maxcy, Wilson, Babuš) have recently been ever more focused on the epidemiology and extension of the definition of noncontagious diseases (malignant diseases, diseases of the circulatory system, mental disorders, traumatism, malnutrition). Among the central nervous system diseases, cerebrovascular diseases occupy the leading position, and every research in the field contributes to the solution of stroke issues.

The latest concepts on stroke prevention attract ever more interest. The high incidence, prevalence and economic cost of stroke make it amenable to prevention. The recent preventive approaches to stroke imply two main strategies: mass approach and individual high risk approach.

In mass approach, the objective is to stimulate lifestyle modifications and to moderately lower the level of risk factors in all individuals within a population. Individual high risk approach addresses individuals with high risk factors and implies use of medication such as antihypertensives, statins, etc., in an attempt to reduce the risk of stroke. The two strategies are complementary in the prevention of stroke. Nowadays, the manifestations of stroke can be prevented by acting systematically upon particular factors through national programs for their elimination, by use of preventive measures, and especially by appropriate dietary habits and lifestyle modification. Many studies

U novije vrijeme naši kao i anglosaksonski autori (Maxcy, Wilson, Babuš) daju sve veću važnost epidemiologiji i proširenju definicije nezaraznih bolesti (maligne bolesti, bolesti cirkulacijskog sustava, mentalne bolesti, traumatizam, neishranjenost). Među bolestima središnjega živčanog sustava (SŽS) cerebrovaskularne bolesti zauzimaju vodeće mjesto. Svako njihovo proučavanje predstavlja doprinos rješavanju problematike moždanog udara. Najnovije spoznaje o prevenciji moždanog udara pobuđuju sve veće zanimanje. Visoka incidencija i učestalost te ekonomski troškovi čine moždani udar pogodnim za prevenciju. Najnoviji preventivni pristupi moždanom udaru podrazumijevaju dvije glavne strategije: masovni pristup – čiji je cilj uvoditi promjene načina života i umjereno smanjiti razinu čimbenika rizika u svih pojedinaca u populaciji; i individualni pristup visokog rizika – koji se odnosi na osobe s visokim čimbenicima rizika, a podrazumijeva upotrebu lijekova kao što su antihipertenzivi, statini i dr. u cilju smanjivanja rizika moždanog udara. Ove su dvije strategije komplementarne u prevenciji moždanog udara. Danas se manifestacije moždanog udara mogu spriječiti sistematskim utjecajima na pojedine čimbenike, nacionalnim programima u suzbijanju nekih čimbenika rizika te poduzimanju preventivnih mjera, a osobito načinom prehrane i mijenjanjem životnih navika. Mnogobrojna istraživanja ukazala su na postojanje čimbenika rizika koji uvjetuju razvoj i ishod moždanog udara. Ti bi se čimbenici mogli podijeliti u dvije

have pointed to the existence of risk factors influencing the development and outcome of stroke. These factors can be divided into two groups: intrinsic and extrinsic risk factors.

Intrinsic risk factors include arterial hypertension, cardiac diseases, diabetes mellitus, adiposity, hematocrit impairment, increased fibrinogen, increased blood lipids, and advanced atherosclerosis. Extrinsic risk factors are cigarette smoking, alcohol consumption, physical inactivity, weather factors, inappropriate dietary habits, and some drugs.

According to Bonita, a neuroepidemiologist, the etio-pathogenesis of stroke can be chronologically reduced to two events: it is primarily underlain by genetic predisposition, superimposed by the extrinsic factors.

Arterial hypertension is the major risk factor for the development of cerebrovascular disease. Framingham study has shown that subjects with established hypertension are at a twofold risk of stroke than the subjects with normal blood pressure, and in those with borderline values of blood pressure the risk of stroke is greater by 50%. Dyslipidemia is a well established risk factor for coronary diseases, however, its association with stroke remains obscure, perhaps due to the heterogeneous nature of stroke. The HDL cholesterol fraction has an inverse effect on the development of atherosclerosis, whereas an increase in LDL fraction directly correlates with the incidence of cardiac diseases.

Cigarette smoking causes lesion of the arterial wall endothelium and elevation of the carboxyhemoglobin concentration in the blood, which in turn reduces the transfer of oxygen to the cells and leads to hypoxia. Cigarette dependence leads to LDL increase and HDL decrease in the blood, whereas cessation of smoking results in regression of atherosclerosis and thus in stroke risk reduction.

Accordingly, it is concluded that the prevention of cardiac diseases should be added to the overall efforts in stroke prevention, because there is a strong inter-relationship between stroke and cardiac diseases.

All physicians, especially those in primary health care, should receive additional training in medicamentous and nonmedicamentous modalities of preventive action, especially on the high importance of systematic blood pressure control, through comprehensive programs warning of the detrimental effects of cigarette smoking, excessive alcohol consumption; dietetic counseling; pharmacologic aspects of blood lipid lowering agents; and on all elements of healthy lifestyle such as regular physical activity. The more so, physicians should be intensely trained in establishing correct indications for the use of anticoagulant and antithrombotic therapy, and for carotid endarterectomy in cardiovascular patients as well as for stroke prevention.

skupine, tj. na unutarnje čimbenike rizika u koje ubrajamo arterijsku hipertenziju, srčane bolesti, šećernu bolest, adipozitet, promjene hematokrita, povišenu razinu fibrinogena, povišene masnoće u krvi, uznapredovalu aterosklerozi; te vanjske čimbenike rizika kao što su pušenje, konzumacija alkohola, tjelesna neaktivnost, meteorološki čimbenici, nepravilna prehrana, uzimanje nekih lijekova. Zanimljiv je stav neuroepidemiologa Bonite koji kronologiju etiopatogeneze moždanog udara svodi na dva zbivanja: prvenstvena je osnova genetska predispozicija na koju se nadopunjuju vanjski čimbenici. Arterijska hipertenzija najznačajniji je čimbenik rizika za pojavu cerebrovaskularnih bolesti. Framinghamska studija ukazuje na to da osobe s ustanovljenom hipertenzijom imaju dvostruko veći rizik za moždani udar nego one s normalnim tlakom. Oni koji su na granici arterijske hipertenzije imaju 50% veći rizik za moždani udar. Dislipidemija je dobro utemeljen čimbenik rizika za koronarne bolesti, ali je njezina povezanost s moždanim udarom ostala nejasna, možda zbog heterogene naravi udara. Frakcija kolesterola HDL ima obrnut utjecaj na razvoj ateroskleroze, dok povišenje frakcije LDL izravno utječe na incidenciju bolesti srca. Prilikom pušenja dolazi do oštećenja endotela arterijske stijenke, a povećava se koncentracija karboksihemoglobina u krvi, što smanjuje prijenos kisika do stanica i uvjetuje hipoksiju. Ovisnost o pušenju dovodi do povišenja LDL-a i sniženja HDL-a u krvi, a pri prestanku pušenja dolazi do regresije ateroskleroze, a time i do smanjenja rizika. Zaključujemo kako bi sveopćim nastojanjima trebalo pridružiti i prevenciju razvoja srčanih bolesti, s obzirom na to da su moždani udar i srčane bolesti u visokoj međuovisnosti. Svi liječnici, poglavito oni u primarnoj zdravstvenoj zaštiti, trebali bi se dodatno obrazovati o medikamentnim i nemedikamentnim načinima preventivnog djelovanja, pogotovo o važnosti sustavne kontrole krvnog tlaka, sveobuhvatnim programima koji upozoravaju na štetnost pušenja i prekomjerne konzumacije alkohola, dijetetskim savjetovanjem, te o farmakološkom značenju uzimanja lijekova koji snižavaju masnoće u krvi i drugim načinima vođenja zdravog života kao što je redovita tjelovježba. Štoviše, liječnici bi se trebali intenzivno obrazovati u postavljanju pravilnih indikacija za primjenu antikoagulantne i antitrombotske terapije, zatim o indikacijama za karotidnu endarterektomiju kod kardiovaskularnih bolesnika, kao i radi prevencije moždanog udara.

Srednjoškolce i mladi odrasle ljude treba biti posebno upozoravati na štetnost pušenja i to bi ih saznanje trebalo obeshrabiliti u stvaranju navike pušenja. Obrazovanje treba biti povezan s pravnim i ekonomskim mjerama koje podupiru masovni pristup prevenciji.

Teenagers and young adults should be specially addressed by warnings on the harmful effects of cigarette smoking, which information should discourage them to develop smoking habit. Education should be accompanied by legal and economic measures that support the mass approach to stroke prevention.

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## THE ROLE OF MEDIA IN STROKE PREVENTION

### ULOGA MEDIJA U PREVENCIJI MOŽDANOG UDARA

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Not received  
Nije primljeno

## ANTIOXIDANTS AND DIET IN THE PREVENTION OF Cerebrovascular Disorders

### ANTIOKSIDANSI I NAČIN PREHRANE U PREVENCIJI Cerebrovaskularnih oštećenja

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The causal relationship between the type of diet and development of stroke has not been fully investigated. Large ecologic studies indicate that excessive intake of dietary fat could be associated with an increased risk of

Neposredna povezanost uzimanja određene vrste hrane i nastanka moždanog udara još uvijek nije dovoljno istražena. Velike ekološke studije ukazuju na to da prekomjerno uzimanje masnoća u hrani nosi povišen rizik za

stroke and coronary ischemic disease. The Framingham study, on the other hand, has found an inverse correlation between dietary fat and ischemic stroke. In addition to fat, large quantities of salt in the diet increase the risk of stroke due to the blood pressure elevation. Another dietary ingredient that may influence circulatory disease is elevated homocystein. The Framingham study has demonstrated that folate, and vitamin B12 and B6 deficits are the most common cause of hyperhomocysteinemia in the risk groups. According to case-control studies, substitution of B6 vitamin may decrease the risk of stroke. Daily dietary intake of fruit and vegetables may have a favorable effect in the prevention of stroke, because they contain antioxidants (vitamins C and E, and provitamin A) that neutralize free radicals after LDL cholesterol oxidation and thus prevent the occurrence of atherosclerotic plaques.

moždani udar i koronarnu srčanu bolest. Framinghamska studija pak ukazuje na obrnutu povezanost između masnoća u prehrani i nastanka ishemijskog moždanog udara. Uz masnoće, povećano soljenje hrane povećava rizik moždanog udara, jer dovodi do hipertenzije. Sljedeći čimbenik u prehrani koji može nepovoljno djelovati na cirkulacijske bolesti je povišeni homocistein. Framinghamska studija pokazuje da je manjak folata, vitamina B 12 i B 6 najčešći uzrok povišenja homocisteina u ugroženim skupinama. Također, nadoknada vitamina B6 može, prema kontroliranim kliničkim studijama, smanjiti rizik za moždani udar. Uzimanje voća i povrća u svakodnevnoj prehrani može povoljno djelovati u prevenciji moždanog udara. Ove namirnice sadrže antioksidanse (vitamini C i E, provitamin A) koji djeluju na slobodne radikale nastale oksidacijom LDL kolesterola i tako sprječavaju aterosklerotske plakove.

## PHYSICAL ACTIVITY IN THE PREVENTION OF STROKE

### TJELESNA AKTIVNOST U PREVENCIJI MOŽDANOG UDARA

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The term physical activity refers to muscle work with a corresponding increase in energy consumption above the level at rest. In industrialized countries, physical work has been vanishing due to mechanization and robotics, and physical inactivity is becoming an important risk factor for the development of many chronic diseases. It is estimated that at least 50% of changes attributed to aging in the population of the industrialized world are caused by atrophy due to inactivity. It is disturbing to learn that in developed countries, 60% to 85% of adults live a sedentary style of life. There is strong scientific evidence for the association between the level of physical activity and health, and most studies demonstrate an association of regular exercise with a decrease in the incidence of coronary heart disease, non-insulin dependent diabetes mellitus, colon carcinoma, and osteoporosis and its clinical manifestations.

Regular physical activity of appropriate type, intensity, duration and frequency improves physical ability, pri-

Pojam tjelesne aktivnosti odnosi se na mišićni rad s odgovarajućim povećanjem energetske potrošnje iznad razine mirovanja. U visokoindustrijaliziranom svijetu tjelesni rad iščezava pred mehanizacijom i robotikom, a tjelesna neaktivnost postaje važan rizični čimbenik za razvoj mnogih kroničnih bolesti. Smatra se da je najmanje pedeset posto promjena koje se pripisuju starenju u populaciji razvijenog svijeta uzrokovano atrofijom uslijed neaktivnosti. Stoga zabrinjava podatak da u razvijenim zemljama 60% do 85% odraslih žive sedanternim načinom života. Postoje brojni znanstveni dokazi o povezanosti razine tjelesne aktivnosti i zdravlja, a najviše je radova koji dokazuju povezanost redovite tjelovježbe i smanjenja incidencije morbiditeta od koronarne bolesti srca, šećerne bolesti neovisne o inzulinu, karcinoma debelog crijeva te osteoporoze i njezinih kliničkih manifestacija. Redovita tjelesna aktivnost odgovarajuće vrste, intenziteta, trajanja i učestalosti poboljšava fizičku sposobnost, ponajprije poboljšanjem učinkovitosti transportnog sustava za kisik, boljim utroškom

marily by improving the efficiency of the oxygen transport system, better utilization of energy substances, and improvement of the nervous system regulatory mechanisms. Aerobic capacity of highly active persons decreases by only 1% - 2% *per* decade of life, whereas in physically inactive individuals this decrease is twofold.

The favorable effects of physical activity on the human body reflect in the following: physical activity results in body weight reduction; in combination with appropriate dietary habits it helps in longterm body weight regulation; protects from the development of atherosclerosis; modifies lipoprotein profile by increasing HDL cholesterol and decreasing serum triglycerides; improves the metabolism of carbohydrates and lowers serum insulin; lowers systemic blood pressure at rest and on exercise; reduces adrenergic consequences of stress; decreases platelet aggregation and increases fibrinolysis; protects bone mass and provides protection from osteoporosis; improves mobility, strength and endurance; improves the mood and stimulates self-confidence.

For the physical activity to be really useful it should be regular, frequent (at least twice a week, or daily at best), of appropriate intensity (mostly moderate and/or modified according to the criteria of the individual's physiologic age), and of appropriate duration. At least 30 minutes of movement are recommended, including activities that imply the work of large muscle groups for a longer period of time and chosen according to the subject's or patient's health condition and preferences: walking, fast walking, swimming, cycling, gardening, house work, climbing stairs instead of using elevator, etc.

Literature data on the effect of physical activity on the primary and secondary prevention of stroke are controversial, however, most prospective studies have shown that physical activity reduces the risk of stroke. Results of the studies suggest these beneficial effects to be present in both sexes, in both young and elderly individuals, and in those with or without previous coronary disease. Sport activities are not mentioned as absolutely necessary, as a moderate level of physical activity can be sufficient to achieve a significant reduction in the risk of stroke and cardiovascular risk in general.

energetskih tvari te poboljšanjem regulacijskih mehanizama živčanog sustava. Aerobni kapacitet visoko aktivnih osoba smanjuje se samo 1%-2% za svako desetljeće života, dok je u tjelesno neaktivnih osoba ovaj pad višestruko veći. Pozitivni učinci tjelesne aktivnosti na ljudski organizam ogledaju se u slijedećem: tjelesna aktivnost utječe na smanjenje tjelesne težine, a udružena s pravilnom prehranom pomaže u njezinoj dugoročnoj kontroli, te štiti od razvoja ateroskleroze; mijenja lipoproteinski profil povećanjem koncentracije HDL kolesterola i smanjenjem razine serumskih triglicerida; poboljšava metabolizam ugljikohidrata i snižava inzulin u serumu; snižava sistemski krvni tlak u mirovanju i za vrijeme napora; smanjuje adrenergične posljedice stresa; smanjuje agregaciju trombocita i povećava fibrinolizu; čuva koštanu masu i štiti od osteoporoze; poboljšava pokretljivost, snagu i izdržljivost, poboljšava raspoloženje i potiče samopouzdanje. Da bi tjelovježba bila korisna ona mora biti redovita, učestala (najmanje dva do tri puta na tjedan, najbolje svakodnevno), odgovarajućeg intenziteta (najčešće umjerenog i/ili prilagođenog prema kriterijima fiziološke starosti osobe) te odgovarajućega trajanja. Preporučuje se barem 30 minuta kretanja, odnosno aktivnosti koje uključuju rad velikih mišićnih skupina kroz duže vrijeme, a odabiru se prema zdravstvenom stanju i sklonostima osobe odnosno bolesnika: pješaćenje, brzo hodanje, plivanje, vožnja biciklom, vrtlarjenje, obavljanje kućanskih poslova, uporaba stubišta umjesto lifta i sl. Literaturni podaci o utjecaju tjelesne aktivnosti na primarnu i sekundarnu prevenciju moždanog udara su kontroverzni. Ipak, većina prospektivnih studija pokazala je da fizička aktivnost smanjenjuje rizik za moždani udar. Rezultati provedenih studija ukazuju na to da je ta korist prisutna u oba spola, u mlađih i starijih osoba, kao i u osoba s ili bez prethodne koronarne bolesti. Pritom se ne navode športske aktivnosti kao neophodne. Umjerena razina tjelesne aktivnosti može biti dovoljna za postizanje značajnog smanjenja rizika od moždanog udara, kao i općenito smanjenja kardiovaskularnog rizika.

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## DIAGNOSIS OF STROKE DIJAGNOSTIKA MOŽDANOG UDARA

### CLASSIFICATION, CLINICAL SIGNS AND SYMPTOMS OF STROKE

### KLASIFIKACIJA I KLINIČKA SLIKA MOŽDANOG UDARA

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Stroke is a clinical syndrome characterized by an acute loss of focal brain function lasting for more than 24 hours or leading to death, which is thought to be due to either spontaneous hemorrhage into or over the brain substance (primarily intracerebral or subarachnoid hemorrhage, i.e. hemorrhagic stroke) or inadequate blood supply to a part of the brain as the result of low blood flow, thrombosis or embolism associated with diseases of the blood vessels, heart or blood (ischemic stroke, cerebral infarction). Transient ischemic attack (TIA) of the brain is the same event as ischemic stroke as defined above, but the symptoms resolve within 24 hours. Once the diagnosis of a TIA or stroke has been established, the next step is to localize the part of the brain and vascular system that has been affected. This depends on the basic knowledge of neuroanatomy, cerebrovascular anatomy and common clinical stroke syndromes.

#### Carotid and Vertebrobasilar Territory Ischemia

Blood supply to the brain is delivered by the two internal carotid and two vertebral arteries, which anastomose at the base of the brain to form the circle of Willis. The carotid artery system supplies the anterior two-thirds of the brain (anterior circulation), and the vertebrobasilar arterial system supplies the posterior third of the brain (posterior circulation).

Moždani udar je klinički sindrom uzrokovan akutnim gubitkom moždane funkcije koji traje dulje od 24 sata ili dovodi do smrti, a nastaje zbog spontanog krvarenja (intracerebralnog ili subarahnoidnog) ili pak moždane ishemije uzrokovane hemodinamski, trombozom ili embolijom, povezano s promjenama na samim krvnim žilama ili srčanom bolešću (ishemijski moždani udar – moždani infarkt). Tranzitorna ishemijska ataka (TIA) mozga je ustvari isto zbivanje kao ishemijski moždani udar, ali se simptomi povlače unutar 24 sata. Kada se postavi dijagnoza TIA-e ili moždanog udara, sljedeći korak je ustanoviti mjesto u mozgu i arteriju koji su zahvaćeni. To ovisi o bazičnim spoznajama o neuroanatomiji, cerebrovaskularnoj anatomiji i sindromima koji nastaju kod moždanog udara.

#### Ishemija u karotidnom i vertebrobazilarnom slivu

Mozak krvlju opskrbljuju dvije unutarnje karotidne i dvije vertebralne arterije koje anastomoziraju na bazi mozga tvoreći Willisov krug. Karotidne arterije opskrbljuju krvlju prednje dvije trećine mozga (prednja cirkulacija), a vertebrobazilarni sustav opskrbljuje krvlju stražnju trećinu mozga (stražnja cirkulacija). Okluzija unutarnje karotidne arterije, ako je simptomatska, obično daje simptome ishemije teritorija srednje moždane arterije, ali oftalmična i prednja moždana arterija mogu također biti uključene, ovisno o kolateralnoj cirkulaciji. Okluzija unutarnje karotidne

Internal carotid artery occlusion, if symptomatic, usually produces symptoms of ischemia in the middle cerebral artery territory, but the ophthalmic and anterior cerebral artery territories can also be involved, alone or in combination with middle cerebral artery, depending on collateral supply. The occlusion of internal carotid artery may cause monocular blindness or altitudinal field defect; contralateral hemiparesis; hemisensory loss; dysphasia or aphasia (dominant hemisphere); contralateral foot and leg weakness, abulia, incontinence.

Vertebrobasilar territory ischemia includes a combination of symptoms: tetraparesis, diplopia, vertigo, cortical blindness, cerebellar ataxia.

More often than not, it is difficult to be certain which arterial territory is involved in an ischemic event of the brain. This is because certain pathways receive their blood supply from both the carotid and vertebrobasilar arteries at different levels. Symptoms and signs that occur with carotid and vertebrobasilar ischemia include hemiparesis, hemisensory deficit, dysarthria.

### Stroke Syndromes

These syndromes are based on clinical features but can be further refined, if necessary by CT imaging. They provide valuable information about the anatomical and vascular location, etiology, and prognosis of the stroke. Common clinical stroke syndromes are:

- TACS, total anterior circulation syndrome – about 20% of cases
- PACS, partial anterior circulation syndrome – about 30% of cases
- LACS, lacunar syndrome – about 25% of cases
- POCS, posterior circulation syndrome – about 25% of cases
- about 1% of stroke patients do not fit any of these syndromes

### Boundary (Border) Zone Infarctions

Boundary (border) zone infarcts are infarcts in the border zones between arterial territories. There are three major boundary zones, which lie between:

- the superficial territories of the middle cerebral artery and anterior cerebral artery in the frontoparasagittal region (anterior boundary zone)
- the superficial territories of the middle cerebral artery and posterior cerebral artery in the parieto-occipital region (posterior boundary zone)
- the superficial medullary penetrators and deep lentikulostriate territories of the middle cerebral artery in the paraventricular white matter of the corona radiata (subcortical boundary zone)

arterije može uzrokovati monokularno sljepilo, ispad vidnog polja, kontralateralnu hemiparezu, hemihipesteziju, disfaziju ili afaziju, slabost kontralateralne noge ili stopala, abuliju, inkontinenciju. Ishemija u vertebrobazilarnom području uključuje kombinaciju simptoma: tetraparezu, diplopiju, vertigo, kortikalno sljepilo, cerebelarnu ataksiju. Najčešće je teško sa sigurnošću utvrditi koja je arterija uzrok ishemijske, jer su pojedini dijelovi mozga opskrbljeni krvlju iz karotidnog i vertebrobazilarnog sliva. Simptomi koji su prisutni i u slučajevima karotidne i vertebrobazilarne ishemijske su: hemipareza, hemihipestezija, dizartrija.

### Sindromi kod moždanog udara

Sindromi nastali moždanim udarom zasnivaju se na kliničkoj slici i mogu se redefinirati pomoću kompjutorizirane tomografije mozga. Oni daju informaciju o anatomskoj i vaskularnoj lokalizaciji lezije, etiologiji i prognozi. Najčešći klinički sindromi kod moždanog udara su:

- TACS – totalni anteriorni cirkulacijski sindrom, u oko 20% slučajeva;
- PACS – parcijalni anteriorni cirkulacijski sindrom, u oko 30% slučajeva;
- LACS – lakunarni cirkulacijski sindrom, u oko 25% slučajeva;
- POCS – posteriorni cirkulacijski sindrom, u oko 25% slučajeva.
- Oko 1% bolesnika s moždanim udarom ne odgovara niti jednom od ovih sindroma.

### Moždani infarkti graničnih područja

Infarkti graničnih područja su infarkti u graničnim zonama između dvaju arterijskih teritorija. Postoje tri glavna granična područja:

- granični (površni) teritoriji srednje moždane arterije i prednje moždane arterije u frontoparasagitalnoj regiji (prednja granična zona);
- površni teritorij između srednje i stražnje moždane arterije u parietookcipitalnoj regiji (stražnja granična zona);
- površni teritorij penetrantnih arterija i dubokih lentikulostriatalnih grana srednje moždane arterije u periventrikularnoj bijeloj moždanoj tvari (subkortikalna granična zona).

Moždani infarkti u graničnim područjima uglavnom su uzrokovani smanjenim protokom krvi koji može nastati zbog naglog pada tlaka (kao kod srčanog aresta) ili pak kod okluzije unutarnje karotidne arterije.

Boundary zone infarcts are usually caused by low flow to the brain. This usually occurs in sudden profound systemic hypotension or internal carotid artery occlusion.

## NEUROIMAGING (CT AND MRI) IN THE DIAGNOSIS OF STROKE

### “NEUROIMAGING” METODE (CT I MRI) U DIJAGNOSTICI MOŽDANOG UDARA

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From 1973, when computed tomography (CT) was first employed in diagnostic work-up of brain diseases, it has become widely used in patients with vascular brain lesions. The roles of CT are multiple: visualization of the ischemic process in its early stage; evaluation of the lesion; follow-up; and detection of possible complications. Other imaging techniques are used in stroke evaluation, however, CT remains the first modality in most cases and institutions.

CT technique has been significantly improved and refined over the past three decades: the number of detectors as well as spatial resolution have increased, greatly improving the image quality and thus visualization of anatomical and pathological details. With the introduction of spiral and multislice scanners, the imaging time has become significantly shorter, with additional capabilities such as CT angiography (CTA).

Early visualization of lesions by CT or magnetic resonance imaging (MRI) is crucial for modern approach to stroke, and the decision for thrombolytic or more conservative treatment is based on the imaging findings.

The basic signs of an acute (<24 h) cerebral infarct in the middle cerebral artery (MCA) territory are: hyperdense MCA, loss of the basal ganglia details, disappearance of the insular ribbon, and asymmetrical narrowing of the cortical sulci. In a significant proportion of patients, CT remains negative in the first 12 hours of the infarct.

Od 1973. godine kada je kompjutorizirana tomografija (CT) uvedena u dijagnostiku bolesti mozga, ona postaje metodom izbora pri zbrinjavanju i liječenju bolesnika s poremećajima moždane cirkulacije. Primarne su uloge ove metode vizualizacija ishemijskog procesa u što ranijoj fazi bolesti; procjena procesa; praćenje tijeka bolesti; te procjena mogućih komplikacija. Danas se u dijagnostici moždanog udara rabe i druge tehnike slikovnog prikaza, no CT i dalje ostaje metoda kojom se započinje neuroradiološka obrada u većini slučajeva i ustanova. S vremenom je CT tehnički znatno unaprijeđen i usavršen: povećani su broj detektora i prostorna rezolucija, čime je znatno poboljšana kvaliteta snimaka, a time i vizualizacija anatomskih i patoloških detalja. Uvođenjem spiralnih i višeslojnih (*multislice*) skenera vrijeme pretrage je znatno skraćeno, uz dodatne nove mogućnosti, kao što je CT angiografija (CTA). Što ranija vizualizacija lezija primjenom CT-a ili magnetske rezonance (MRI) ima ključnu ulogu u suvremenoj dijagnostici moždanog udara, pri odlučivanju za trombolitičnu ili konzervativnu terapiju. Temeljni znaci akutnog (<24 h) moždanog udara u opskrbnom području arterije cerebri medije (ACM) su: hiperdensna ACM, brisanje strukture bazalnih ganglija i korteksa inzule, te asimetrično sužavanje kortikalnih sulkusa. Značajan postotak bolesnika ima uredan CT mozga u prvih 12 sati nakon nastanka inzulta. Za razliku od CT-a, u većine bolesnika s inzultom ACM područja proces se prikazuje MRI-om

As opposed to CT, most patients with an MCA stroke have positive findings on MRI within the first 24 hours. Cortical edema, loss of gray matter/white matter differentiation (on T2-weighted, PD, and FLAIR images), hyperdense MCA on FLAIR images, and increased contrast opacification of the vessels in the infarcted area due to slower flow are typically seen within the first few hours. Diffusion-weighted (DWI) and perfusion-weighted (PWI) imaging techniques provide sensitivities and specificities that are almost 100% already in the first hour of the stroke onset.

In the subacute phase (day 3-21) secondary hemorrhage occurs in approximately 15% of MCA strokes. Gyri-form contrast enhancement is usually most prominent from the third to seventh day of the stroke onset. Wallerian degeneration along the affected corticospinal tract may be visualized starting from four weeks of the stroke onset. Encephalomalacia is encountered in the chronic phase.

Isolated infarct in the territory of the anterior cerebral artery (ACA) is a rare event (<1%), more commonly seen with internal carotid artery occlusions. It may occur as a consequence of trauma or space-occupying lesions. Posterior cerebral artery (PCA) infarcts may be secondary to transtentorial herniation, and in young patients may indicate vasculitis.

Basilar artery occlusion has frequent fatal outcomes, and is characterized by infarcts scattered throughout the infratentorial and posterior cerebral artery territories.

Laminar necrosis is a specific entity, corresponding to cortical infarcts that preserve some layers, with a characteristic high signal intensity on T1-weighted and FLAIR images, which may be misinterpreted as areas of hemorrhage.

Venous infarcts are most commonly caused by thrombosis of the venous sinuses, which is usually readily identified on MRI. These infarcts do not correspond to arterial territories, and are commonly hemorrhagic, bilateral, and subcortical.

unutar prvih 24 sata. Unutar nekoliko sati od pojave simptoma tipično se nalaze kortikalni edem, gubitak diferencijacije sive i bijele tvari (na T2-mjerenim, PD i FLAIR snimkama), hiperdensna ACM na FLAIR snimkama, te povećano nakupljanje kontrasta u krvnim žilama infarciranog područja uslijed sporijeg protoka. Difuzijske (*diffusion-weighted*, DWI) i perfuzijske (*perfusion-weighted*, PWI) tehnike pružaju osjetljivost i specifičnost od gotovo 100% već u prvom satu nakon nastupa inzulta. U subakutnoj fazi (3.-21. dan) pri obliteraciji ACM u oko 15% slučajeva dolazi do sekundarnog krvarenja. Giriformna kortikalna imbibicija kontrastom je obično najizraženija od trećega do sedmoga dana bolesti. Wallerianova degeneracija duž zahvaćenog kortikospinalnog puta može biti prikazana od četvrtog tjedna bolesti. Encefalomalacija se nalazi u kroničnoj fazi. Izolirani infarkt opskrbnog područja a. cerebri anterior (ACA) je rijedak (<1%), češće se nalazi pri okluziji a. karotis interne. Može se javiti kao posljedica traume ili ekspanzivnih procesa. Infarkti u području a. cerebri posterior (ACP) znaju nastati kao posljedica transtentorijske hernijacije, a u mladih bolesnika mogu ukazivati na vaskulitis. Okluzija a. basilaris često dovodi do smrtnog ishoda, a obilježena je infarktima razbacanim po infratentorijskim te ACP opskrbnim područjima. Laminarna nekroza je poseban entitet koji odgovara kortikalnom infarktu s očuvanim pojedinim slojevima korteksa, a pokazuje znakovit visoki signal na T1-mjerenim i FLAIR snimkama, što se ponekad pogrešno tumači kao područje krvarenja. Venski infarkti su najčešće izazvani trombozom venskih sinusa, što se obično lako dijagnosticira MRI-om. Ovi infarkti ne odgovaraju arterijskim opskrbnim područjima, a često su hemoragijski, obostrani i smješteni subkortikalno.

## ANGIOGRAPHY IN THE DIAGNOSIS OF STROKE

### ANGIOGRAFIJA U DIJAGNOSTICI MOŽDANOG UDARA

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Stroke is a heterogeneous group of cerebrovascular disorders with a wide array of clinical manifestations. The pathology, etiology, prognosis and treatment vary according to type of stroke. The term stroke covers the following entities: ischemic cerebral infarct (ICI) (~80%); primary intracerebral hemorrhage (PICH) (~15%); subarachnoid hemorrhage (SAH) (~5%); and venous thrombosis (VT) (~1%).

In the diagnosis and therapy planning for stroke patients, angiography plays a major role. The first useful angiography of cerebral vessels was performed in 1927. The method has improved with the development of contrast media (CM). The first CM was ionic and characterized by high osmolarity. Currently used CM is non-ionic, isoosmolar, and with minor side effects. The method is widely used in connection with computer assistance and digitalization of radiological equipment, which reduces the amount of CM and radiation dose.

Direct percutaneous carotid angiography was for long the only approach to visualize brain arteries. It was associated with numerous complications such as arterial wall damage, subintimal injection of CM, and intimal lesions. In the beginning of the 1950s, transcatheter angiography was first mentioned in the literature. From late 1970s, with the development of catheters, guiding wires and introducers, direct puncture has been losing battle.

#### Angiography in Ischemic Cerebral Infarct

In spite of the advent of new methods (CDI, MRA, CTA), intra-arterial angiography remains a useful tool for visualization of cervicocranial blood vessels. Arteriosclerosis is highly associated with ICI. During angiographic procedure of intracranial arteries, it is obligatory to visualize extracranial arteries as well. The aims of cerebral angiography in arteriosclerosis are: to determine the degree of stenosis; to demonstrate the associated 'tandem' lesions at the siphon and intracranial branches; to visualize possible collateral circulation; and to prove plaque ulceration. A stenosis >70% is considered hemodynamically signifi-

Moždani udar (MU) je heterogena skupina cerebrovaskularnih poremećaja sa širokom kliničkom slikom. Različita je patologija, etiologija, prognoza i liječenje. Vrste MU su: 1. moždani ishemijski infarkt (MII) (~80%); 2. primarno unutar moždano krvarenje (PUMK) (~15%); 3. subarahnoidno krvarenje (SAH) (~5%); 4. venske tromboze (VT) (~1%). U dijagnostici i planiranju liječenja MU angiografska dijagnostika ima veliku ulogu. Prva upotrebljena angiografija krvnih žila mozga učinjena je 1927. godine. Metoda je napredovala s razvojem kontrastnih sredstava (KS). Stara KS bila su jonska, visoko osmolarna. Suvremena su nejonska, izoosmolarna, minimalnih nuspojava. Raširenosti metode doprinijela je kompjutorizacija i digitalizacija radiološke opreme dovodeći do značajnog smanjenja u potrošnji KS, kao i smanjenju zračenja. Direktna perkutana karotidna angiografija dugo vremena bila je jedini pristup arterijskom stablu, s brojnim komplikacijama (oštećenje stijenke arterije, subintimna injekcija KS, lezije intime). Početkom 1950.-ih transkateterska angiografija spominje se u literaturi. Od kasnih 1970.-ih unapređenjem katetera, žica vodilica i uvodnica potiskuje direktnu punkciju.

#### Angiografija u MII

Usprkos novim metodama (CDI, MRA, CTA) intrarterijska angiografija ostaje pouzdana metoda prikaza cervikokranijalnog arterijskog stabla. Ateroskleroza je usko povezana s ishemijskom bolešću mozga. U okviru angiografije intrakranijske cirkulacije neophodna je i obrada ekstrakranijskog dijela arterija. Cilj angiografije kod ateroskleroze moždanih arterija je: 1. odrediti stupanj suženja; 2. prikazati eventualne udružene («tandem») lezije u području sifona i intrakranijskih ogranaka; 3. dokazati moguću kolateralnu cirkulaciju; 4. dokazati ulceraciju postojećeg plaka. Suženje >70% smatra se hemodinamski značajnim. U intrakranijskim ogranacima ateroskleroza se prikazuje kao neravnost kontura, suženje arterija, elongacija i izvijuganost, te prisutnost vretenastih aneurizmatičkih proširenja. Angiografija se izvodi u hiperakutnoj

cant. Arteriosclerosis of intracranial branches is seen as irregularities of the contours, elongation and tortuosity, and as fusiform aneurysms. In the hyperacute phase of ischemic infarct, angiography is performed only in case of intra-arterial fibrinolytic therapy. Angiographic signs of infarction are: occlusion of blood vessel; slow blood flow with prolonged arterial phase; collateral, retrograde filling; zones of poor perfusion; luxury perfusion; early venous drainage; and edema induced mass-effect. Collateral circulation is a major angiographic sign in chronic infarction.

### Angiography in Primary Intracerebral Hemorrhage

The most common cause of PICH is arterial, and in rare cases venous bleeding. Bleeding localizations are in the parenchyma or near meninges. It is very common in tumors, metastases and angioma. The main angiographic sign of bleeding is displacement and bowing of arterial and venous branches. It is uncommon to visualize extralumination of CM. The role of angiography in PICH diagnosis is minor after the invention of CT and MRI, which can even detect the etiology of bleeding.

### Angiography in Subarachnoid Hemorrhage

Nearly 90% of nontraumatic SAH are caused by ruptured aneurysms. Aneurysms can be saccular, fusiform and dissecting. The angiographic picture is related to the shape. In case of saccular aneurysm, it is obligatory to visualize the neck for the operative procedure planning. The entire intracranial circulation must be examined to show one or all aneurysms. In case of multiple aneurysms, the localization of rupture should be verified by additional neuroimaging methods (CT, MRI).

### Angiography in Venous Thrombosis

VT of the brain is the most underdiagnosed cause of neurologic deficit. VT begins with incomplete occlusion of dural sinuses by a clot and continues with complete sinus thrombosis and propagation of thrombosis to the bridging veins. On angiography, VT appears like an empty canal with dilatation of dural veins. Thrombosis of cortical veins looks like cordlike contrast collections 'hanging in space'. The lack of CM filling of the Galeni vein indicates thrombosis of deep cerebral veins.

fazi infarkta samo u slučaju intraarterijske fibrinolitične terapije. Angiografski znaci akutnog infarkta su: 1. okluzija krvne žile; 2. usporen protok s produženim arterijskim pražnjenjem; 3. kolateralno, retrogradno punjenje; 4. zone ispada perfuzije; 5. luksuzna perfuzija; 6. rana venska drenaža; 7. *mass-effect* uzrokovan edemom. U kroničnom infarktu glavni angiografski znak je kolateralna cirkulacija.

### Angiografija u PUMK

PUMK je najčešće arterijskog, a rijetko venskog podrijetla. Lokalizacija može biti u parenhimu ili uz ovojnice mozga. Često se javlja uz tumore, metastaze ili iz angioma. Glavni angiografski znak je potiskivanje i lučno napinjanje arterijskog i venskog stabla. Vrlo rijetko prikaže se ekstraluminacija KS. Uloga angiografije u dijagnostici PUMK je minorna nakon uvođenja CT i MRI kojima se otkriva i etiološki čimbenik.

### Angiografija u SAH

Približno 90% netraumatske SAH uvjetovano je aneurizmama. Mogu biti sakularne, fuziformne i disecirajuće. Angiografska slika vezana je uz oblik. U slučaju sakularne aneurizme nužno je dokazati položaj vrata radi planiranja operacijskog zahvata. Nužan je prikaz potpune intrakranijske cirkulacije zbog prikaza jedne i/ili svih aneurizama. Lokalizacija rupturirane aneurizme u slučaju nekoliko aneurizama vezana je za dodatne dijagnostičke metode (CT, MR).

### Angiografija u VT

Venskookluzivna bolest mozga je prilično rijetko dijagnosticiran razlog neurološkog deficita. Počinje nepotpunim zatvaranjem duralnog sinusa ugruškom, a nastavlja se potpunom trombozom i širenjem tromba u mosne vene. Angiografski trombozirani sinus izgleda poput praznog kanala uz proširene duralne vene. Trombozirane kortikalne vene su vrpčaste, u "zraku viseće" strukture. Ispad prikaza vene Galeni upućuje na trombozu dubokih cerebralnih vena.

## THE ROLE OF ULTRASOUND IN THE DIAGNOSIS OF CEREBROVASCULAR DISORDERS

### ULOGA ULTRAZVUKA U DIJAGNOSTICI MOŽDANIH KRVOŽILNIH POREMEĆAJA

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Stroke outcome depends on emergency management, stroke type, and therapeutic procedures. The focus is set on the early detection of patients with known risk factors, whereby ultrasound methods play a major role. Ultrasound is a noninvasive method that can define with high accuracy the risk factors for development of a specific stroke subtype. By means of extracranial color Doppler, the appearance and type of atherosclerotic plaques can be visualized, and thus also the degree of stenosis and plaque stability by means of three- and four-dimensional ultrasound. Other types of inflammatory neurovascular diseases can also be visualized as well as nonatherosclerotic vasculopathies and dissections, which can develop independently of the aforementioned diseases. High resolution B-mode ultrasound enables visualization of early atherosclerosis (carotid intima-media thickness).

By means of transcranial Doppler and transcranial color-coded Doppler sonography, occlusive intracranial disease can be localized. Also, hemodynamic redistribution in extracranial occlusive disease can be assessed, and recanalization of the occluded vessel can be observed. In hemorrhagic strokes, suspicion of vascular malformations with fragile vessels and bleeding into the intracerebral and subarachnoidal space can be set. The time course and therapy can be monitored. The development of softwares has led to a wide variety of applications. High intensity transient signals (HITS) can be detected as a risk for embolization in cardiac diseases (left atrium thrombus, patent foramen ovale) and vascular diseases (unstable carotid stenosis, aortic arch, dissection). The possibility of vasoreactivity testing enables evaluation of the vasomotor capacity. The development of ultrasonographic techniques has led to easy and noninvasive assessment of individuals at a risk of stroke.

Ishod moždanog udara ovisi o hitnosti zbrinjavanja, tipu moždanog udara, kao i o terapijskim postupcima. Stoga se težište postavlja na rano otkrivanje bolesnika s čimbenicima rizika za njegov nastanak. Tu imaju važnu ulogu ultrazvučne metode. Ultrazvučne metode su neinvazivne metode kojima se mogu ustanoviti čimbenici rizika za razvoj pojedinoga podtipa moždanog udara. Ekstrakranijskim obojenim doplerom može se ustanoviti izgled i vrsta aterosklerotskih plakova, površina i stupanj stenoze žile, te stabilnost plaka upotrebom tro- i četverodimenzionalnog ultrazvuka. Prikazuju se druge upalne bolesti krvožilja, neaterosklerotske vaskulopatije i disekcije žila koje se mogu javiti nevezano uz neku od prije navedenih bolesti. Visokorezolutni B-mod ultrazvuk pruža dodatne informacije o početnim aterosklerotskim promjenama (debljina intime i medije stijenke karotidne arterije). Transkranijalnim doplerom i transkranijalnim obojenim doplerom se može locirati mjesto okluzivne promjene, ustanoviti preraspodjela hemodinamike kod ekstrakranijskih okluzivnih promjena i pratiti rekanalizaciju okludirane arterije. Kod hemoragijskih moždanih udara postavlja se sumnja na postojanje krvožilnih tvorbi kod kojih nastaje pucanje žila i krvarenje u intracerebralni i subarahnoidni prostor, te prati razvoj i liječenje. Razvoj programa doveo je do mogućnosti monitoriranja embolijskih signala kao rizika za embolizaciju kod kardijalnih bolesti (tromb lijevog atrija, postojanje otvorenog foramen ovale), te bolesti krvožilja (stenoze nestabilnim plakovima karotidnih arterija, luka aorte, disekcije istih žila). Moguće je testiranje vazoreaktivnosti u procjeni vazomotornog kapaciteta. Razvoj ultrazvučnih tehnika doveo je do olakšane i neinvazivne procjene ispitanika s rizikom za nastanak moždanog udara.

## THERAPY OF STROKE TERAPIJA MOŽDANOG UDARA

### TREATMENT OF ACUTE STROKE

### TERAPIJA AKUTNOG MOŽDANOG UDARA

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The main goal of treatment is to lessen the brain damage due to ischemia and the neurologic deficit due to stroke. The zone encircling the ischemic part with partial disturbance of energy capacity is called penumbra. Most important is to start the treatment as early as possible in specialized intensive care units (ICU), within 3 to 6 hours from the onset of disease. The main aim is to confirm the diagnosis and exclude the states that can show the features of stroke, where the use of specific treatment can even worsen the outcome. The current treatment for ischemic stroke is limited to a small number of specific therapeutic procedures and a very narrow time frame. Still many medications are used due to erroneous belief that they are effective and safe for the patient. All present knowledge takes as an imperative the early beginning of treatment, imposing the need of a highly important task of educating both health personnel and the population at large.

Smanjiti oštećenje mozga zbog ishemije i neurološkog deficita kao posljedice moždanog udara osnovni je cilj liječenja. Zona koja okružuje središnji dio ishemije u kojoj je prisutan djelomičan poremećaj energetske kapaciteta naziva se penumbrom. Najvažnije je početi liječenje što ranije u specijaliziranim jedinicama intenzivnog liječenja (JIL), i to unutar 3 do 6 sati od početka bolesti. Osnovno je potvrditi dijagnozu te isključiti stanja koja mogu pokazivati kliničku sliku moždanog udara u kojima primjena specifičnog liječenja može i pogoršati ishod. Sadašnje liječenje akutnog ishemijskog udara ograničeno je na malen izbor specifične terapije i vrlo uzak vremenski prozor. Još uvijek se mnogi lijekovi rutinski primjenjuju u pogrešnom vjerovanju da su djelotvorni i sigurni za bolesnika. Sva dosadna saznanja uvode kao imperativ što raniji početak liječenja, a to kao najvažniji zadatak nameće obrazovanje kako zdravstvenog osoblja tako i šire javnosti.



## NEUROSURGICAL MANAGEMENT OF INTRACRANIAL ANEURYSMS AND INTRACEREBRAL HEMATOMAS

### NEUROKIRURŠKO LIJEČENJE INTRAKRANIJSKIH ANEURIZAMA I INTRACEREBRALNIH HEMATOMA

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Intracranial aneurysms and intracerebral hematomas are the most common reason for neurosurgical management of cerebrovascular disorders. Intracranial aneurysms are baggy-like, saccular, elongated, fusiform or dissecting lesions of the wall of cerebral vessels, which are caused by either structural changes of the vessel wall or by hemodynamic factors. Rupture of intracranial aneurysms causes subarachnoid hemorrhage, an emergency clinical state characterized by specific clinical manifestations.

After the initial event, hemorrhage into the subarachnoid space, a pathophysiologic sequence of events will occur that are responsible for the clinical picture and determine the outcome of the pathologic event. Patients with subarachnoid hemorrhage are endangered not only by the initial hemorrhage but also by its complications such as rehemorrhage, vasospasm and hydrocephalus.

The most important question in treating the patient with subarachnoid hemorrhage, from the neurosurgical point of view, is when to operate. The answer is almost never unambiguous and is influenced by several factors. Factors that are analyzed when making the decision on timing of operation are: possibility of rehemorrhage, presence of vasospasm and possibility of its evolution, patient's clinical state, amount of blood in the subarachnoid space verified by CT scan, age of patient, associated conditions, brain tissue edema verified by CT scan, localization and shape of aneurysm, presence of intraparenchymal bleeding or other complications, operating team experience, and finally the time that has elapsed from the onset of subarachnoid hemorrhage to hospital admission.

Considering all these as well as our own 22-year clinical experience and a series of 932 intracranial aneurysms operated on, we have come to some conclusions that are elaborated in the guidelines for the management of such lesions (guidelines for operative treatment of patients with subarachnoid hemorrhage caused by rupture of intracranial aneurysm).

Najčešći supstrat neurokirurškog liječenja cerebrovaskularnih poremećaja su intrakranijske aneurizme i intracerebralni hematomi. Intrakranijske aneurizme su vrećaste – sakularne, izdužene - fuziformne ili disecirajuće promjene na stijenkama cerebralnih krvnih žila, koje su uzrokovane bilo strukturnim promjenama same stijenke krvnih žila bilo hemodinamskim čimbenicima. Ruptura intrakranijskih aneurizama uzrokuje subarahnoidno krvarenje, hitno kliničko stanje obilježeno specifičnim kliničkim pojavnostima. Nakon početnog zbivanja, krvarenja u subarahnoidni prostor, slijedi čitav niz patofizioloških zbivanja koja uzrokuju kliničku sliku i određuju ishod patološkog zbivanja. Bolesnici sa subarahnoidnim krvarenjem patofiziološki su ugroženi kako samim početnim krvarenjem tako i njenim komplikacijama kao što su ponovljeno krvarenje, vazospazam i hidrocefalus. S neurokirurškog stajališta, u liječenju bolesnika sa subarahnoidnim krvarenjem najvažnije je pitanje kada takvog bolesnika operirati. Odgovor gotovo nikada nije jednoznačan, a na njega utječu brojni čimbenici. Čimbenici koje analiziramo pri donošenju odluke o vremenu operacije su sljedeći: mogućnost ponovljenog krvarenja, prisutnost vazospazma, kao i mogućnost njegova razvoja, bolesnikovo kliničko stanje, količina krvi u subarahnoidnim prostorima dokazana CT snimanjem, bolesnikova dob, postojeće bolesti, edem moždanog tkiva dokazan CT snimanjem, zatim lokalizacija i oblik same aneurizmatске tvorbe, prisutnost intraparenhimnog krvarenja ili drugih komplikacija, iskustvo operacijskog tima i na kraju vrijeme koje je proteklo od napadaja subarahnoidne hemoragije do prijma bolesnika. Uzimajući u obzir navedeno, kao i naše vlastito 22-godišnje iskustvo uz 932 operirane intrakranijske aneurizme došli smo do zaključaka koji su izneseni u smjernicama za liječenje ovih tvorbi (smjernice za operacijsko liječenje bolesnika sa subarahnoidnim krvarenjem uzrokovanim rupturom intrakranijske aneurizme). Prateći najnovije trendove u liječenju intrakranijskih aneurizama, u suradnji s neuroradiolozima Kli-

Following recent trends in the management of intracranial aneurysms, in cooperation with neuroradiologists from the Department of Radiology of our hospital, we have introduced interventional-endovascular methods in the treatment of such lesions in our standard clinical practice. Gradually, with technology development, new techniques of selective endovascular obliteration of aneurysms by filling their lumen with various materials, usually 'coils', thereby preserving blood flow in the artery where the aneurysm is developing, have become available. The initial period of the use of endovascular techniques was reserved for patients at a greater risk for open surgery, therefore other treatment options were considered. In this phase, candidates for endovascular treatment were mostly patients with worse clinical state, older age, and difficult localization of aneurysm; in short, patients in whom open surgery was not the first choice method of treatment.

With technology development and evaluation of initial results, some advantages of endovascular treatment over open surgery have been established. Therefore, if there is indication, the procedure will be performed immediately upon diagnostic angiography and verification of intracranial aneurysm.

The cerebrovascular team consists of a neurosurgeon, an interventional radiologist and an anesthesiologist. When the diagnosis is made, the team decides on the treatment options by evaluating particular parameters, and further procedures and treatment options are discussed.

We think that such a multidisciplinary approach in the analysis of the pathologic substrate and planning of treatment options is the only right approach in the management of this challenging condition.

Concerning the neurosurgical treatment of spontaneous intracerebral hematomas, the guidelines are precise. Intracerebral hematomas are divided according to their volume and localization. So we can state the following:

- hematomas in the posterior fossa and cerebellum are the conditions that require emergency surgical treatment,
- patients with hematomas that occupy 4% to 12% of the brain hemisphere (lobar hematoma) and their clinical picture is worsening can be operatively treated,
- comparably, poor results are obtained by operative and conservative treatment of hematomas with a volume exceeding 12% of the hemisphere, and
- patients with hematomas of a volume of 1% to 4% and are localized in basal ganglia, thalamus and capsula interna, are conservatively treated.

Recently, intracerebral hematomas are also treated endoscopically or by using neuroradiologic methods, so-called 'open MR assisted neurosurgery'.

ničkoga zavoda za radiologiju naše bolnice uveli smo u našu standardnu kliničku praksu i interventne - endovaskularne metode liječenja ovih tvorba. Naime, razvojem tehnologije postupno se razvijaju nove tehnike selektivne endovaskularne obliteracije samih aneurizmatičkih tvorba metodom njihovog punjenja različitim materijalima – najčešće zavojnicama (*coils*) – uz očuvanje krvnog protoka u glavnoj arteriji na kojoj se aneurizma razvija. U početnom razdoblju primjene endovaskularnih tehnika liječenja ove metode bile su rezervirane za bolesnike kod kojih je neurokirurški rizik bio velik, stoga se pribjegavalo drugim terapijskim opcijama. Tako su u početnoj fazi najčešći kandidati za endovaskularni postupak bili bolesnici lošeg kliničkog stanja, visoke starosne dobi te oni s vrlo teškim lokalizacijama aneurizmatičke tvorbe, dakle, svi oni bolesnici kod kojih operacijska metoda nije bila metoda prvoga izbora. Razvojem tehnologije te procjenom početnih rezultata uvidjelo se da endovaskularni zahvati imaju i određene prednosti nad operacijskim zahvatima. Stoga danas ovaj postupak, ako se za njega postavi indikacija, nastavljamo odmah nakon dijagnostičke angiografije i verifikacije intrakranijske aneurizme, neposredno nakon prijma bolesnika u bolnicu. Formirani cerebrovaskularni tim što ga čine neurokirurg, interventni neuroradiolog te anesteziolog, nakon postavljanja dijagnoze i dokazivanja aneurizme, donosi odluku o načinu liječenja procjenjujući određene parametre, te se donosi odluka o daljnjim postupcima, odnosno načinu liječenja. Mišljenja smo da je ovakav, multidisciplinarni način sagledavanja patološkog supstrata i planiranja terapijskih opcija jedini ispravan način liječenja tako "zahtjevnih" bolesnika. Što se neurokirurškog liječenja spontanijih intracerebralnih hematoma tiče, smjernice su razmjerno precizne. Intracerebralne hematome tako dijelimo s obzirom na veličinu i lokalizaciju, te načelno možemo reći sljedeće:

- hematome stražnje lubanjske jame i malog mozga potrebno je operacijski (hitno) liječiti;
- operacijski možemo liječiti bolesnike s hematomima veličine od 4% do 12% hemisfere (lobarni hematomi) čije je kliničko stanje u pogoršanju;
- operacijsko i konzervativno liječenje daju podjednako loše rezultate u liječenju bolesnika s hematomima veličine preko 12% hemisfere velikog mozga;
- konzervativno liječimo bolesnike s hematomima veličine od 1% do 4% lokalizirane u bazalnim ganglijima, talamusu i kapsuli interni.

U posljednje vrijeme intracerebralne hematome liječimo i endoskopski, tj. uz pomoć neuroradioloških metoda, tzv. "open MR assisted neurosurgery".

## ANTICOAGULANT THERAPY IN THE PREVENTION AND TREATMENT OF STROKE

### ANTIKOAGULANTNA TERAPIJA U PREVENCIJI I LIJEČENJU MOŽDANOG UDARA

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Anticoagulant agents that are used in practice for years, have been the subject of many discussions. In 80% of stroke cases, the underlying causes are ischemic events due to vascular occlusion. Antithrombotic therapy primarily refers to ischemic stroke, however, the risk of intracranial hemorrhage is the main hindrance to the use of antithrombotic drugs in both the prevention and treatment of stroke. Antithrombotic therapy has the crucial role in the prevention of ischemic stroke. The highest risk is associated with the use of thrombolytics. The risk is less pronounced with anticoagulants, and is the least although still present with antiplatelet agents. The treatment of vascular risk factors such as hypertension, cigarette smoking, diabetes mellitus and hyperlipidemia, and the use of antithrombotic agents are the two main approaches in the prevention of primary and secondary stroke. In the use of antithrombotic therapy for prevention of stroke, the absence of cardiogenic embolism should be differentiated from cardioembolic stroke. In primary prevention in noncardiogenic embolism, aspirin is the first choice drug, as it is the only drug that has been studied in primary prevention. The use of aspirin has proved reasonable in patients with atheromas (asymptomatic carotid stenosis) who are at a higher risk of myocardial infarction and cardiac death than of brain infarction. Secondary prevention primarily includes patients who have suffered first ever transient ischemic attack (TIA) or stroke and are at a high risk of any vascular event, mostly second stroke or myocardial infarction. Many questions remain open in the field, e.g., optimal aspirin doses, choice of the most appropriate antithrombotic agent or a combination of agents, and efficacy of novel antithrombotic drugs such as GP IIb/IIIa antagonists. Other antithrombotic drugs in use are ticlopidin, clopidogrel and dipyridamole. Until more data on the efficacy and safety of anticoagulants become available, antiplatelet drugs remain the drugs of choice in the prevention of atherothrombotic stroke and in patients without the cardiac origin of embo-

Antikoagulacije se u praksi primjenjuju već niz godina i predstavljaju predmet brojnih rasprava. U 80% slučajeva moždanog udara (MU) nalaze se ishemijski događaji zbog okluzije krvne žile. Antitrombotsko liječenje odnosi se prije svega na ishemijski MU, ali je rizik od intrakranijskog krvarenja osnovna prepreka uporabi antitrombotskih lijekova kako u prevenciji MU tako i liječenju bolesnika s MU. Antitrombotska terapija ima temeljnu ulogu u prevenciji ishemijskog MU. Najveći je rizik s tromboliticima, nešto manji s antikoagulansima i najmanji, ali ipak postoji s antitrombocitnim lijekovima. Liječenje vaskularnih rizičnih čimbenika kao što su hipertenzija, pušenje, dijabetes i hiperlipidemija, i uporaba antitrombotskih lijekova dva su glavna pristupa prevenciji primarnog i sekundarnog MU. Kod primjene antitrombotskog liječenja u prevenciji MU treba razlikovati odsutnost kardiogenog embolizma od kardiembolijskog MU. U primarnoj prevenciji kod nekardiogenog embolizma na prvom mjestu od lijekova je aspirin koji je i jedino proučen u primarnoj prevenciji. Pokazalo se da je razumno primijeniti aspirin kod ateroskih bolesnika (asimptomatska stenoza karotida) i onih s većim rizikom infarkta miokarda i srčane smrti negoli infarkta mozga. Sekundarna prevencija prije svega obuhvaća bolesnike koji su imali prvu tranzitornu ishemijsku ataku (TIA) ili MU i pod velikim su rizikom od bilo kojeg vaskularnog događanja, najčešće drugog MU ili infarkta srca. Ostaju otvorena brojna pitanja koja uključuju optimalne doze aspirina, izbor najboljeg antitrombotskog lijeka ili kombinacija lijekova i učinkovitost novih antitrombotskih lijekova kao što su antagonisti GP IIb/IIIa. Od drugih antitrombotskih lijekova primjenjuju se tiklopidin, klopidogrel i dipiridamol. Dok ne bude još podataka o učinkovitosti i sigurnosti primjene antikoagulanata, antitrombocitni lijekovi ostaju lijek izbora u prevenciji atherotrombotskog MU odnosno u bolesnika bez srčanog izvora embolizma. Prevencija kardiembolijskog MU temelji se prvenstveno na specifičnom liječenju srčane bolesti i uporabi oralnih antikoagulanata.

lism. The prevention of cardioembolic stroke is primarily based on the specific treatment of cardiac disease and administration of oral anticoagulants. This refers to all high risk origins of cardiac embolism (mitral stenosis, mechanical artificial valves, recent myocardial infarction, mural thrombosis of the left ventricle, atrial fibrillation). Atrial fibrillation is the most common origin of cardiac embolism and is responsible for some 50% of all cardiac emboli. In atrial fibrillation, oral anticoagulants are the drugs of choice. Studies have shown that aspirin and oral anticoagulants are efficacious in the primary and secondary stroke prevention in patients with atrial fibrillation, however, oral anticoagulants are associated with a higher risk of hemorrhage. On prescribing the drug, assessment of the risk of embolic stroke and of massive hemorrhage should always be individualized. In other cardiac diseases, the antithrombotic strategy of stroke prevention is based on the principle of balancing the risk and embolism. The decision on the administration of antithrombotic therapy should be made individually for each case, weighing the risk of early occurrence of new emboli and of intracerebral hemorrhage, which mostly depends on the size of infarct. In the antithrombotic treatment of acute ischemic stroke, antithrombotic drugs, anticoagulants, thrombolytics and fibrinogen reducing agents have been used. In contrast to prevention, where an international consensus has been achieved, considerable differences related to antithrombotic strategy exist in the management of acute ischemic stroke. Numerous studies have shown that aspirin is the only antiplatelet drug that has been evaluated in the treatment of acute stroke. Of the new antiplatelet agents for the treatment of acute ischemic stroke that are currently under study, mention should be made of the GP IIb/IIIa receptor antagonists. Concerning anticoagulants, various heparins have been used, e.g., nonfractionated heparin, low molecular weight heparin (LMWH), and heparinoid (Organon). It has been shown that low doses of low molecular heparin should be used in patients with hemiplegia and limited mobility for the prevention of deep venous thrombosis and pulmonary embolism. Thrombolysis has brought revolution in the management of stroke, because it has demonstrated that the major goal of recovery is the fastest possible restitution of blood flow. Streptokinase, intravenous recombinant tissue plasminogen activator (IV rt-PA), and intra-arterial prourokinase are being used. Intra-arterial prourokinase (IA) is an alternative to intravenous thrombolysis, however, cerebral angiogram is required to identify the site of occlusion and to allow for the agent to reach the clot. Recently, Ancrod, a viper venom protease, a fibrinogen degrading agent, has also been investigated. The antithrombotic strategy in the management of acute

Ovo se odnosi na sve visoko rizične izvore kardijalnog embolizma (mitralna stenoza, mehaničke umjetne valvule, nedavni infarkt srca, muralna tromboza lijeve klijetke, atrijska fibrilacija). Atrijska fibrilacija je i najčešći izvor kardijalnog embolizma i odgovorna je za oko 50% svih embolusa srca. Kod atrijske fibrilacije oralni antikoagulansi su lijek izbora. Istraživanja su pokazala da su aspirin i oralni antikoagulansi učinkoviti u primarnoj i sekundarnoj prevenciji ishemijskog MU u bolesnika s atrijskom fibrilacijom, ali su oralni antikoagulansi udruženi s većim rizikom krvarenja. Kod primjene lijeka uvijek treba u svakom pojedinom slučaju procijeniti pitanje rizika embolijskog MU i rizika opsežnijeg krvarenja. Kod ostalih srčanih bolesti antitrombotska strategija prevencije MU temelji se na načelu balansiranja rizika i embolije. Odluka o primjeni antitrombotske terapije se mora donijeti na temelju svakog pojedinačnog slučaja važući rizik rane pojave novih embolusa s rizikom intracerebralnog krvarenja koje najviše ovisi o veličini infarkta. U antitrombotskom liječenju akutnog ishemijskog MU u uporabi su antitrombotski lijekovi, antikoagulansi, trombolitici i lijekovi koji smanjuju fibrinogen. Nasuprot prevenciji gdje postoji opće međunarodno slaganje glede liječenja akutnog ishemijskog inzulta, postoje važne razlike u antitrombotskoj strategiji. Niz ispitivanja dosad je pokazao da je aspirin jedini antitrombocitni lijek koji je procijenjen u liječenju akutnog ishemijskog MU. Od novijih antitrombocitnih lijekova u liječenju akutnog ishemijskog MU, koji su još u ispitivanju, mogu se spomenuti antagonisti receptora GP IIb/IIIa. Od antikoagulanata u primjeni su različiti heparini: nefrakcionirani heparin, heparin niske molekularne težine (LMWH) i heparinoid (Organon). Pokazalo se da niske doze heparina, i to niskomolekularnog, treba rabiti u bolesnika s hemiplegijom i ograničenom pokretljivošću u prevenciji duboke venske tromboze i plućne embolije. Tromboliza je u MU revolucija, jer je pokazala kako je bitan cilj oporavka hitno uspostavljanje tijeka krvi. U uporabi su streptokinaza, intravenski rekombinacijski aktivator tkivnog plazminogena (IV rt-PA), intraarterijska prourokinaza. Intraarterijska prourokinaza (IA) alternativa je intravenskoj trombolizi, no potreban je angiogram mozga kako bi se odredilo mjesto okluzije te kako bi se sredstvo dopremilo u ugrušak. U novije vrijeme u ispitivanju je Ancrod, proteaza zmijske, sredstvo koje razgrađuje fibrinogen. Antitrombotska strategija akutnog liječenja ishemijskog MU razlikuje se ovisno o dostupnosti rt-Pa. U zemljama u kojima nije odobren ili nakon više od 3 sata aspirin je lijek izbora udruženi s niskim dozama LMWH uvijek kada postoji hemiplegija ili ograničena pokretljivost (zbog prevencije duboke venske tromboze i plućne embolije).

ischemic stroke differs according to rt-PA availability. In the countries where rt-PA has not been approved, or after 3 hours of stroke onset, aspirin in combination with low doses of LMWH is the therapy of choice in case of hemiplegia or limited mobility (for the prevention of deep venous thrombosis and pulmonary embolism).

## VASCULAR SURGERY IN STROKE THERAPY

### VASKULARNA KIRURGIJA U TERAPIJI MOŽDANOG UDARA

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Carotid surgery is not just an organ surgery. It is a surgery of the soul and personality which greatly influences the patient's quality of life. Total cost of stroke in the Republic of Croatia is 120.000.000 USD *per* year. The high neurologic morbidity, mortality and social implications point to the importance of the recognition and treatment of carotid disease in order to reduce the rates of stroke. Each year, more than 8000 individuals suffer stroke in Croatia. The real needs of carotid endarterectomy or carotid stenting (CEA/CAS) rise to >2500 operations *per* year. CEA should be a safe operation, with the proportion of stroke and death in the results of 0.5% - 2.5%. The isolated procedure related death rate should be less than 1%. It seems that locoregional anesthesia is most reliable in revealing perioperative neurologic morbidity and in reducing the time of hospital stay. Following endless discussions in the past, in the 1990s it was recognized that surgeons should treat particular subgroups of patients rather than dispute whether or not to operate on.

Prospective randomized studies conducted in the 1980s/1990s have led to the need of achieving multidisciplinary, multicenter consensus on surgical prevention and management of stroke by *evidence based medicine* (EBM). Some recent important events have been stimulated by a great number of multicenter reports following operative procedures in asymptomatic patients, indicating that CEA/CAS can prevent the occurrence of stroke. The latest International Overseas Consensus on the Management of Asymptomatic Carotid Bifurcation Stenosis (Marseilles

Karotidna kirurgija nije tek kirurgija organa. To je kirurgija duše i osobnosti koja značajno utječe na kvalitetu života bolesnika. Ukupni troškovi moždanog udara u Republici Hrvatskoj iznose 120.000.000 USD godišnje. Visok neurološki morbiditet, mortalitet i društvene implikacije ukazuju na važnost prepoznavanja i liječenja karotidne bolesti s ciljem smanjenja stope moždanog udara. U Hrvatskoj svake godine >8000 bolesnika doživi ishemijski moždani udar. Stvarna potreba karotidne endarterektomije ili karotidnog stentinga (CEA/CAS) raste do >2500 operacija godišnje. CEA treba biti sigurna operacija, s udjelom moždanog udara i smrti u rezultatima od 0,5%-2,5%. Izdvojena smrtnost zahvata trebala bi biti manja od 1%. Čini se da lokoregionalna anestezija najpouzdanije otkriva periooperacijski neurološki morbiditet i skraćuje vrijeme bolničkog liječenja. Poslije beskonačnih rasprava u prošlosti, u devedesetima je izronila spoznaja da kirurzi trebaju liječiti podskupine bolesnika, a ne sporiti se treba li operirati ili ne. Prospektivne, randomizirane studije u '80./'90.-tim dovele su nas do potrebe za multidisciplinarnim, multicentričnim konsenzusima o kirurškoj prevenciji i liječenju moždanog udara, medicinom temeljenom na dokazima (*Evidence Based Medicine*). Nedavni važni događaji potaknuti su velikim brojem multicentričnih izvještaja nakon operacija u asimptomatskih bolesnika. Oni ukazuju na činjenicu da CEA/CAS mogu sprječavati moždani udar. Noviji Međunarodni prekomorski konsenzusi o liječenju asimptomatske stenoze karotidne bifurkacije (Marseilles '98., Zagreb '00., Cipar '01., London '02.) napravili su značajan korak napri-

'98, Zagreb '00, Cyprus '01 and London '02) meetings have made a significant step forward by introducing the qualitative in addition to the existing quantitative plaque analysis. During the past decade, the fast development of noninvasive diagnosis has imposed the unavoidable reevaluation of arteriography as a gold 'standard'. Since 1995, the non-operator dependent criteria have been defined in the ultrasound (US) and computed tomography (CT) diagnosis. Health Care Commissions have begun granting authorization to Excellence Centers in US Diagnosis. In 2002, carotid disease has been categorized into asymptomatic or symptomatic, liable to longitudinal CEA, liable to eversion endarterectomy (CEEA), and selected cases for CAS. Among stroke patients, care should be especially paid to those with stroke in progression. These patients should be evaluated according to the principles of emergency vascular surgery. The US criteria indicating the need of CEA are: >25% echolucency, heterogeneity, thin cap with a necrotic nucleus, hemorrhage into the plaque, and lipemic, ulcerated and ramified plaque. Although CEA should be the only true prevention of stroke, the number of operations in asymptomatic patients is on a gradual increase. The reasons for this lie in difficulties to get a significant number of properly randomized patients, wide variation in vital statistics, fear from neurologic complications, poor understanding of the possibilities of US diagnosis, and traditional way of thinking.

CEEA appears to be a useful alternative to 'classic' CEA in patients with preserved collateral circulation, those at risk of restenosis, those free from visible cerebral infarction, and those with distal stenosis but not to the base of the skull. CEEA is an acceptable procedure in the hands of a surgeon who has mastered it under appropriate supervision and in hospitals where patients are followed-up by duplex sonography and their results are published in professional periodicals.

In search for alternative treatment modalities, comparison of percutaneous transluminal carotid angioplasty (PTCA) and CEA conducted during the 1995-1997 period showed the former to be associated with a higher rate of neurologic complications and early restenosis. The results on CAS, obtained between 1996 and 1998 in selected patients, were comparable with CEA results, however, with a considerably poorer results after secondary stenting. The agents for cerebral protection, introduced in Europe towards the end of 1990s, have significantly improved CAS results. According to the New York CBAS Consensus from 1999 and Parma MET Criteria from 2001, CAS is not advisable in low risk patients, petrified bifurcation, floating and acute thrombus, and in patients with associated common carotid artery stenosis. The recom-

jed uvodeći kvalitativnu uz dosadašnju kvantitativnu analizu plaka. U proteklom desetljeću brzi razvoj neinvazivne dijagnostike nametnuo je neizbježnu reevaluaciju arteriografije kao "zlatnog standarda". Od 1995. kriteriji neovisni od očitavača (*non-operator dependent criteria*) definirani su u UZV i CT dijagnostici. Povjerenstva za zdravstvo (*Health Care Commissions*) započela su odobravanja Centara izvrsnosti u ultrazvučnoj dijagnostici. U 2002. godini karotidna bolest dijeli se na asimptomatsku ili simptomatsku, pogodnu za longitudinalnu CEA, pogodnu za everzionu endarterektomiju (CEEA) i odabrane slučajeve za CAS. U bolesnika s moždanim udarom osobitu pozornost zahtijevaju oni s udarom u progresiji. Takovi bolesnici procjenjuju se prema načelima hitne vaskularne kirurgije. Ultrazvučni kriteriji koji indiciraju potrebu za CEA su: >25% eholucencnosti, heterogenost, tanki pokrov s nekrotičnom jezgrom, hemoragija u plak, lipemični, ulcerirani i razlistani plak. Premda bi CEA trebala biti jedina prava prevencija moždanog udara, broj operacija u asimptomatskih bolesnika polagano raste. Razloge treba tražiti u poteškoćama da se postigne značajan broj pravilno randomiziranih bolesnika, u širokoj varijaciji vitalne statistike, strahu od neuroloških komplikacija, smanjenom razumijevanju mogućnosti UZV i tradicionalnom načinu mišljenja. CEEA izgleda korisna alternativa "klasičnoj" CEA u bolesnika s očuvanim kolateralnim krvotokom, u bolesnika s rizikom razvoja restenoze, u onih bez vidljive moždane infarkcije i u bolesnika s distalnom stenozom, ali ne do baze lubanje. CEEA je prihvatljiv zahvat u rukama kirurga koji je izučio operaciju pod nadgledanjem mentora i u bolnicama koje prate bolesnike dupleks-sonografijom i publiciraju njihove rezultate. Tražeći alternativne mogućnosti liječenja, u razdoblju 1995.-1997. perkutana transluminalna karotidna angioplastika (PTCA) uspoređena s CEA imala je više neuroloških komplikacija i veći udio rane restenoze. Rezultati CAS-a 1996.-1998. u izabranih bolesnika bili su usporedivi s CEA, ali sa znatno lošijim rezultatom nakon sekundarnog stentinga. Sredstva cerebralne zaštite uvedena u Europi krajem '90.-tih značajno su unaprijedila rezultate CAS-a. Prema New York CBAS Consensus 1999. i Parma MET Criteria 2001, CAS nije pogodan u bolesnika niskog rizika, kod petrificirane bifurkacije, u bolesti s flotirajućim i akutnim trombom i u bolesnika s pridruženom stenozom zajedničke karotidne arterije. Preporučljive indikacije za CAS su: stenoza izvorišta ili debla zajedničke karotide, bolesnik visokog rizika, visoka stenoza unutarne karotide i vrat nedostupan za otvorenu kirurgiju. Široko prihvaćena, ali ne poduprta prema EBM, indikacija za CAS je glatka karotidna restenoza. Ako pozornost obratimo na zajedništvo karotidne i koronarne bolesti (u RH 18%-22% koronarnih bolesnika), iznose se detaljni kriteriji za CEA/CAS u tak-

mended indications for CAS are: stenosis of the origin or trunk of the common carotid, high risk patients, high stenosis of internal carotid, and neck inaccessibility for open surgery. A widely adopted but not EBM supported indication for CAS is smooth carotid restenosis.

Considering the carotid and coronary comorbidity (18% - 22% of coronary patients in Croatia), detailed criteria for CEA/CAS in these patients, categorized into 8 distinctly defined subgroups, are presented.

At the end, a number of questions remain open, such as: What to do with a carotid stenosis <50% which causes neurologic deficit? What are the newly recognized plaque features associated with neurologic deficit? How to improve cerebral protection? What is the optimal proportion of CEA/CAS? What is the best medicamentous therapy for carotid disease? Gene therapy and carotid disease?

ovih bolesnika razdijeljenih u 8 jasno definiranih podskupina. Na kraju preostaje podosta pitanja. Neka su: Što uraditi s karotidnom stenozom ispod 50% koja uzrokuje neurološki deficit? Koje su nove osobitosti plaka povezane s neurološkim deficitom? Kako možemo unaprijediti cerebralnu zaštitu? Koji je optimalan udio CEA/CAS? Što je najbolja medikamentna terapija karotidne bolesti? Genska terapija i karotidna bolest?

## SURGICAL PROCEDURES ON EXTRACRANIAL CEREBRAL ARTERIES IN THE PREVENTION OF STROKE

### KIRURŠKI POSTUPCI NA EKSTRAKRANIJSKIM CEREBRALNIM ARTERIJAMA U PREVENCIJI MOŽDANOG UDARA

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The main aim of all surgical procedures on extracranial cerebral arteries (endarterectomy, anatomic and extra-anatomic autologous and alloplastic bypasses, transpositions and arterial resections with neoanastomoses, and endovascular procedures such as PTA with or without stent) is prevention of stroke or its severe recurrence. Surgical treatment is mostly indicated in order to eliminate the symptoms of transient cerebral dysfunction, which frequently predict a stroke, but also in asymptomatic patients threatened by advanced stenoses, obliterations, or ulcerated plaques.

In almost 90% of cases, the cause of cerebrovascular disease (CVD) is atherosclerosis or occlusive arterial dis-

Svi kirurški postupci na ekstrakranijskim cerebralnim arterijama (endarterektomija, anatomska i ekstraanatomska autologna i alopastična premoštenja, transpozicije i resekcije arterija s neoanastomozama, te endovaskularni zahvati, kao PTA s ili bez stenta) imaju prvenstveno preventivan koncept liječenja s ciljem sprječavanja moždanog udara ili njegovog težeg recidiva. Kirurško je liječenje najčešće indicirano kako bi se otklonili simptomi prolaznih disfunkcija mozga, koji često nagovještavaju moždani udar, ali i kod asimptomatskih bolesnika koje ugrožavaju uznapredovale stenoze, obliteracije ili ulcerirani plakovi. Naime, u gotovo 90% slučajeva uzrok je cerebrovaskularne bolesti (CVB) ateroskleroza, odnosno okluzivna bolest arterija,

ease, and rarely various arteritides. Other diseases and conditions that may cause CVD and are surgically managed include kinkings, tortuosities, elongations and loop formations of cerebral arteries, congenital anomalies (aplasia, hypoplasia, atypical course and origin of blood vessels), arterial compression, traumatic and iatrogenic lesions of blood vessels, fibromuscular dysplasia, and various aneurysms.

Acute or progressive stroke can only exceptionally and in specific circumstances be surgically treated. An operation on cerebral arteries is mostly irrational because of the high mortality rates (8% - 28%). At this stage of CVD (clinical stage III), conservative treatment yields better results. In stroke patients, urgent neurologic treatment and management in neurologic intensive care units are indicated.

Presentation is made of all surgical procedures, with special reference to carotid endarterectomy, which has received the highest level of scientific validation based on the results of randomized multicenter studies in terms of longterm therapeutic results and indication criteria.

From 1970 till August 15, 2002, a total of 1993 carotid endarterectomies in 1879 patients (114 patients were operated on bilaterally) were performed at the Department of Vascular and Endovascular Surgery, University Department of Surgery, Sestre milosrdnice University Hospital, Zagreb, making the greatest number of patients operated on at a single institution in Croatia. There were 518 female and 1361 male patients, mean age  $64.1 \pm 8.4$  (range 38-98) years. The results comparable with the best results reported in the world were achieved using the maximally standardized operative technique, adjusted to the nosogenic type of carotid bifurcation on the basis of our own hemodynamic research.

rijetko i razni arteritisi. Ostale bolesti i stanja koje mogu biti uzrokom CVB i predmet kirurškog liječenja su: presa-vinuća (*kinking*), tortuoziteti, elongacije i petljaste tvorbe mozgovnih arterija, prirodene anomalije (aplazija, hipoplazija, atipičan tijek i polazište krvnih žila), kompresija arterija, traumatske i jatrogene ozljede krvnih žila, fibromuskularna displazija i razne aneurizme. Akutni ili progresivni moždani udar samo se iznimno i u posebnim okolnostima može kirurški liječiti, a zbog visokih stopa smrtnosti (8%-28%) operacija na mozgovnim arterijama najčešće je iracionalna. U tom su stadiju CVB (III. klinički stadij) bolji rezultati konzervativnog liječenja. Kod bolesnika s moždanim udarom indiciran je hitan neurološki tretman i liječenje u jedinicama intenzivne neurološke skrbi. Prikazani su svi kirurški postupci s posebnim osvrtom na karotidnu endarterektomiju koja ima najvišu razinu znanstvene valorizacije na temelju rezultata multicentričnih randomiziranih studija glede dugoročnih rezultata liječenja i kriterija indiciranja.

U razdoblju od 1970. do 15. kolovoza 2002. godine na Odjelu za vaskularnu i endovaskularnu kirurgiju Kirurške klinike Kliničke bolnice „Sestre milosrdnice“ ukupno su učinjene 1993 karotide endarterektomije u 1879 bolesnika (114 je bolesnika operirano bilateralno). Srednja dob operiranih iznosi  $64,1 \pm 8,4$  (raspon 38-98) godina. Operirano je 518 žena i 1361 muškarac, što predstavlja najveći broj operiranih u jednoj ustanovi u Hrvatskoj. Maksimalno standardiziranom operacijskom tehnikom koja je na temelju vlastitih istraživanja hemodinamike prilagođena nozogenetskom tipu karotidne bifurkacije postignuti su rezultati usporedivi s najboljima u svijetu.



## REHABILITATION IN STROKE PATIENTS REHABILITACIJA MOŽDANOG UDARA

### REHABILITATION IN STROKE PATIENTS

### REHABILITACIJA BOLESNIKA NAKON MOŽDANOG UDARA

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In stroke patients rehabilitation must be a polyvalent, professionally well organized and economical process. Structural complexity of the central nervous system functions determines to a great extent its potential for regeneration and especially for recovery or restitution of its functions: motor, sensory, intellectual, etc. It is just this complexity, and especially the rising prevalence of stroke, that require a multidisciplinary team work.

The team should be led by a neurologist, who will make the causal and pathophysiological diagnosis and evaluate the prognostic possibilities of the patient, on the basis of the new concepts in neuroscience and neurobiochemical research; then, together with other team members, he will design a gradual program of rational and functional rehabilitation. A plan of work based on the rehabilitation outcome estimate should be developed, the main questions being: Who?, Where?, and When?

The earliest possible, targeted, highly differentiated diagnostic procedures are crucial for accurate evaluation of the type of stroke, which is the basis of the rehabilitation schedule. Rehabilitation is divided into four main stages: early rehabilitation, rehabilitation on vital function stabilization, rehabilitation following physical recovery and partial personal independence of hospital care, and rehabilitation follow-up (on outpatient basis, mobile teams, and community based rehabilitation). The possible use of current methods of functional restorative rehabilitation,

Rehabilitacija oboljelih od moždanog udara mora biti polivalentan, stručno dobro organiziran i ekonomičan proces. Složenost struktura funkcija središnjega živčanog sustava određuje u znatnoj mjeri njegovu sposobnost regeneracije i poglavito oporavka ili ponovnog uspostavljanja (restauracije) njegovih funkcija: motoričkih, osjetilnih, intelektualnih i drugih. Upravo zbog složenosti, a osobito zbog porasta broja oboljelih od moždanog udara potreban je multidisciplinarni "timski" rad. Vođa tima treba biti neurolog koji mora na osnovama novih spoznaja iz neuroznanosti i neurobiokemijskih istraživanja postaviti kauzalnu i patofiziološku dijagnozu i prognostičke mogućnosti bolesnika, te s ostalim članovima tima utvrditi stupnjeviti program racionalne i funkcijske rehabilitacije. Potrebno je razraditi plan organizacije rada koji se zasniva na procjeni ishoda rehabilitacije, a osnovni upiti su: Tko?, Gdje? i Kada?. Ključno pitanje je što ranija, ciljana, visokodiferentna dijagnostička obrada radi procjene tipa moždanog udara, koja je osnova pri izradi plana rehabilitacije. Osnovna podjela je u četiri stupnja: rana rehabilitacija, rehabilitacija pri stabilizaciji vitalnih funkcija, rehabilitacija nakon fizičkog oporavka i djelomične osobne neovisnosti o stacionarnoj medicinskoj skrbi, i praćenje rehabilitacije (ambulantno, pokretni timovi i rehabilitacija u zajednici). Pritom treba procijeniti i mogućnosti eventualne primjene suvremenih metoda funkcijske restaurativne rehabilitacije koju čine kompleksni oblici liječenja, kao implantacija određenih

consisting of complex modes of treatment such as implantation of electrostimulating electrodes, should thereby also be taken in consideration. Also, modification of pathologic functions in order to use them for the establishment of the new form of sensorimotor control should be considered as a modality of modern restorative neurology. This also helps in the sensorimotor function recovery, including affective self-control, whereby the physiotherapeutic, neurosurgical, neuropharmacologic and psychological methods are used in various combinations, depending on the patient condition and stage of rehabilitation.

Besides its early beginning, precise determination of the program of rehabilitation based on the continuous functional diagnosis is another important precondition for a favorable therapeutic outcome of stroke patients.

elektrostimulacijskih elektroda, te modifikacija patoloških funkcija u cilju njihove uporabe radi uspostavljanja novog oblika senzomotorne kontrole kao mogućnost moderne restaurativne neurologije. Ovo je učinkovito jednako za oporavak senzomotornih funkcija, uključujući afektivnu samokontrolu, pri čemu se kombiniraju fizikalno terapijske, neurokirurške, neurofarmakološke i psihološke metode, ovisno o stanju i fazi rehabilitacije. Jedna od važnih pretpostavka za što bolji rezultat liječenja bolesnika s moždanim udarom je ne samo rani početak, nego i precizno postavljanje programa rehabilitacije temeljem kontinuirane funkcijske dijagnostike.

## NEUROPSYCHOLOGICAL EVALUATION OF COGNITIVE FUNCTIONS IN STROKE PATIENTS

### NEUROPSIHOLOGIJSKA PROCJENA KOGNITIVNIH FUNKCIJA NAKON MOŽDANOG UDARA

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Stroke causes significant temporary and permanent disabilities. Besides neurologic deficits, cognitive function impairments have been most extensively investigated. Studies have shown that the most intensive recovery of these impairments occurs within the first three months after the stroke, whereafter residual and mostly permanent deficits persist in one third of stroke patients.

Cognitive impairments may manifest as specific deficits that can be assessed on neurologic examination (e.g., homonymous hemianopia, telegraphic speech), however, they more frequently occur as complex deficits that require neuropsychological evaluation for complete assessment. Neuropsychology deals with the study of connection between the central nervous structures and behavior. Behavior includes three functional systems: cognitive functions, emotionality, and executive or control functions. Cognitive functions have been most thoroughly investigated. Cog-

Moždani udar uzrokuje značajna privremena i trajna onesposobljenja oboljele osobe. Uz neurološka oštećenja najčešće su ispitivani poremećaji kognitivnog funkcioniranja. Istraživanja su pokazala da je njihov najintenzivniji oporavak unutar prva tri mjeseca nakon incidenta, a nakon tog razdoblja u 1/3 slučajeva zaostaju oštećenja koja su onda najčešće i trajna. Kognitivna se oštećenja mogu javiti kao specifični defekti koje je moguće procijeniti tijekom neurološkog pregleda (npr. homonimna hemianopsija, telegrafski govor), ali znatno češće kao kompleksni deficiti za čiju je potpunu procjenu potrebna neuropsihologijska evaluacija. Neuropsihologija se bavi ispitivanjem veze između središnjih živčanih struktura i ponašanja. Ponašanje obuhvaća tri funkcionalna sustava: kognitivne funkcije, emocionalnost i izvršne, kontrolne funkcije. U najvećoj su mjeri ispitivane kognitivne, odnosno spoznajne funkcije. Kognitivno funkcioniranje obuhvaća: receptivne funkcije (spo-

nitive functioning includes receptive functions (ability to receive, classify and integrate information), thinking (ability of organizing and restructuring information), memory and learning (information storage and evoking), and expressive functions (executing or communicating information). In the last century, the interest was mainly focused on the detection of cerebral localization of high mental functions. Over the last two decades, an approach that respects distributed functions has been developed as the result of the new concepts of the human mind functioning, and since recently attempts have been made to unify these two approaches. Localized functions of speech, reading, writing, calculating, and high motor control of execution are located in the dominant hemisphere, whereas visuoperceptive, visuospatial and construction abilities as well as the prosodic aspects of speech are located in the nondominant hemisphere. Distributed cognitive functions are not localized and have a distributed neural basis, e.g., memory, high frontal executive functions, attention and concentration.

Neuropsychological evaluation is an extensive procedure consisting of clinician's observation, a battery of tests and other techniques of examination, and collection of data on the patient's psychosocial and medical history, including data available from the patient's family members, relatives and friends. The data produced by neuropsychological tests should be interpreted at both quantitative and qualitative level, thereby taking each individual's uniqueness in consideration. On the result interpretation, an appropriate basis for comparison should be formed, considering the patient's age, level of education, socioeconomic status, and cultural background, also attempting to define the premorbid level of functioning. Cognitive impairments are quite common sequels of stroke, mostly affecting the functions of memory, attention and concentration, speech, visuoperceptive and construction abilities, and orientation. The systematic overview of the type and grade of cognitive impairments, offered by neuropsychological evaluation, provides data of high relevance for the organization of the process of rehabilitation, assessment of residual abilities for professional functioning and daily living, or evaluation of the conditions required for proper patient care.

Additional studies in the field of cognitive functions and in neuropsychology in general provide a large body of data that may contribute to better understanding of the patients and the nature of their problems, and to ensure conditions for improvement of the patient quality of life.

sobnost primanja, klasificiranja i integriranja informacija), mišljenje (sposobnost organizacije i reorganizacije informacija), pamćenje i učenje (pohrana i evokacija informacija), te ekspresivne funkcije (izvršavanje ili priopćavanje informacija). U posljednjem je stoljeću glavno zanimanje bilo usmjereno na otkrivanje cerebralne lokalizacije viših mentalnih funkcija. Zadnja dva desetljeća, kao rezultat novih spoznaja o funkcioniranju ljudskog uma razvio se pristup koji daje važnost distribuiranim funkcijama, a odnedavno se ova dva pristupa pokušavaju objediniti. Lokalizirane su funkcije govor, čitanje, pisanje, računanje, viša motorna kontrola izvedbe – u dominantnoj hemisferi, a vizuo-perceptivne, vizuo-spacijalne i konstrukcijske sposobnosti, kao i prozodički aspekti govora – u nedominantnoj hemisferi. Distribuirane kognitivne funkcije nisu lokalizirane, imaju distribuiranu neuralnu osnovu, a to su pamćenje, više frontalne izvršne funkcije te pozornost i koncentracija. Neuropsihologijska procjena je opsežan postupak koji se sastoji od opservacije kliničara, primjene baterije testova kao i drugih tehnika ispitivanja, te prikupljanja podataka o psihosocijalnoj i medicinskoj povijesti oboljelog, kao i onih koje može dati obitelj ili bližnji. Podaci koje daju neuropsihologijski testovi moraju biti tumačeni na kvantitativnoj, ali i kvalitativnoj razini uzimajući u obzir jedinstvenost svakog pojedinca. U interpretaciji rezultata potrebno je stvoriti primjerenu osnovu za usporedbu, uzimajući u obzir dob, obrazovnu razinu, socioekonomski status i kulturalni okvir, uz pokušaj određenja premorbidne razine funkcioniranja. Nakon moždanog udara kognitivni poremećaji su česti, a u najvećoj su mjeri pogođeni pamćenje, pozornost i koncentracija, govor, visuoperceptivne i konstrukcijske sposobnosti, te orijentacija. Sistematičan pregled vrste i stupnja kognitivnih oštećenja što ga daje neuropsihologijska evaluacija pruža podatke važne za organizaciju procesa rehabilitacije, procjenu preostalih sposobnosti za profesionalno funkcioniranje kao i svakodnevni život ili ocjenu potrebnih uvjeta zbrinjavanja bolesnika. Daljnja ispitivanja na području kognitivnih funkcija, kao i neuropsihologije uopće daju mnoštvo podataka koji mogu doprinijeti boljem razumijevanju bolesnika, naravi njegovih problema, te stvaranju uvjeta za poboljšanje kvalitete življenja ljudi pogođenih ovom bolešću.

## SPEECH REHABILITATION IN STROKE PATIENTS

### REHABILITACIJA GOVORA NAKON MOŽDANOG UDARA

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Speech function impairment consequential to organic cerebral dysfunction is known to be the most common cognitive deficit encountered in patients with cerebrovascular disease. Aphasia is a frequent sequel of stroke, with a prevalence of as high as 21% - 24% of acute stage patients. In some patients, aphasia shows spontaneous regression, so 10% - 18% of stroke survivors have aphasia (Prins and Vermeulen, 1991).

Aphasia destroys articulated expression, its comprehensiveness, writing and reading, i.e. all four modalities of language activities at all its levels, from phoneme through discourse, from letter through text, from automated through creative expression. The rehabilitation of speech communication is a complex, multidisciplinary and very longlasting process. The principle of the earliest possible introduction of speech therapy has proved useful both in Croatia and worldwide.

Rehabilitation implies not only restitution of the speech-language function but of the complete personality and, if possible, of the patient's living environment. Speech rehabilitation should be initiated immediately, i.e. during the patient's hospital stay as soon as in stable condition. It is needed to prevent fading away of those language functions that have not been damaged but simply blocked by the condition. The loss of traces for auditory, kinesthetic and visual imaging of the word and its perception should be avoided, which can be achieved by early treatment while the physiologic processes are still freshly preserved.

Speech therapy in aphasic patients should rely on the following principles: early rehabilitation of the speech and language; patient motivation and stimulating his active participation in the rehabilitation procedure; appropriate, diagnosis based stimulation; training in those compensatory abilities that will best help in unblocking of particular modalities of the language-speech functions, reading, writing and calculating; providing conditions for speech exercise and complete patient rehabilitation at the hospital, clinic for speech rehabilitation, or in the family; strict-

Poznato je da od svih kognitivnih deficita u cerebrovaskularnim bolestima najčešće susrećemo poremećaj u govornim funkcijama koji je posljedica organske cerebralne disfunkcije. Afazija je česta posljedica moždanog udara, s učestalošću od čak 21% do 24% bolesnika u akutnoj fazi. U određenog broja bolesnika afazija se spontano povuče pa 10%-18% preživjelih bolesnika ima afaziju (Prins i Vermeulen, 1991.). Afazija razara artikulirani izraz, njegovo razumijevanje, pisanje i čitanje, dakle, sva četiri modaliteta jezične djelatnosti na svim njezinim razinama, od fonema do diskursa, od slova do teksta, odnosno od automatiziranog do stvaralačkog izraza. Proces rehabilitacije govorne komunikacije je složen, multidisciplinarni i izrazito dugotrajan. Načelo što ranijeg uvođenja logopedске terapije pokazalo se uspješnim i u nas i u svijetu. Pod rehabilitacijom se ne podrazumijeva samo obnavljanje govorno-jezične funkcije, već i cijele ličnosti i, ako je moguće, i sredine u kojoj bolesnik živi. Logopedska rehabilitacija trebala bi započeti odmah, još dok je bolesnik u bolnici, kada je izvan životne opasnosti. Ovo je potrebno kako ne bi došlo do zamiranja onih jezičnih funkcija koje nisu oštećene, nego samo blokirane uslijed nastalog stanja. Treba izbjeći gubljenje tragova za auditivnu, kinestetičnu i vizualnu predodžbu riječi i njeno zapažanje, a to se postiže ranim tretmanom dok su fiziološki procesi još svježiji. Logopedska terapija afazičara mora počivati na određenim načelima, a to su: rana rehabilitacija jezika i govora; motivacija bolesnika i razvijanje njegovog sudjelovanja u rehabilitacijskom postupku; odgovarajuća stimulacija koja počiva na dijagnostici; vježbanje onih kompenzacijskih mogućnosti koje će najviše pomoći deblokiranju pojedinih modaliteta jezičnog govornih funkcija, čitanja, pisanja i računanja; stvaranje uvjeta za govornu vježbu i potpunu rehabilitaciju bolesnika u bolnici, u logopedskoj ambulanti i u obitelji; strogo individualiziran logopedski tretman zasnovan na naravi bolesti (vrsti i stupnju gubitka govornih i ostalih zdravstvenih funkcija), kao i na tipu ličnosti i njenom ponašanju; neunificirana terapija mora polaziti od intelektualne razine bolesnika, njegovog materinjeg jezika i pozitivnog

ly individualized speech pathology treatment based on the patient's type of disorder (type and grade of the speech and other function impairments), type of personality, and behavioral pattern; nonunified therapy should start from the patient's intellectual level, mother's tongue, positive attitude, and a number of other factors the patient had been regularly using before the disease or playing a major role in his life.

Cooperation with the patient's family is also of paramount importance. The current approaches in the treatment of aphasia include the following: therapy conducted according to psycholinguistic theories; cognitive neurorehabilitation; computer techniques; psychosocial approach; and pharmacotherapy (still in the experimental phase).

A good prognosis of aphasia can usually be made within the first month of stroke onset, depending on the severity of initial disturbances. The prognosis of recovery depends on the patient age and condition, and the etiology and extent of primary lesion. Considerable recovery occurs within the first six months of the deficit onset. Spontaneous recovery from aphasia is most successful during the first three months, however, improvements can also occur later. The prevalence of total recovery varies between 21% and 50%.

Traumatic aphasia recovers faster than vascular aphasia. In spite of abundance literature on the evaluation and treatment of aphasia, little has been reported on therapy termination. Our knowledge based on experience suggests that speech therapy should take as long as any success in the recovery of initial disturbances is recorded (1-3 years) and the patient is motivated for it. Termination of continuous speech therapy has been observed to be followed by stagnation or regression of the recovered disturbances, and patients presented again for speech therapy one year after speech therapy completion.

opredjeljenja, kao i niza drugih činilaca koje je bolesnik prije oboljenja upotrebljavao ili su igrali kakvu značajnu ulogu u njegovom životu. Bitna je još suradnja s obitelji i prihvaćanje afazične osobe od strane obitelji. Aktualni pristupi liječenju afazija uključuju: terapiju vođenu psiholingvističkim teorijama, kognitivnu neurorehabilitaciju, kompjutorske tehnike, psihosocijalni pristup, farmakoterapiju (još na eksperimentalnoj osnovi). Valjana prognoza afazije se može obično postaviti unutar prvog mjeseca nakon moždanog udara, ovisno o jačini početnih smetnji. Za prognozu oporavka važni su dob i zdravstveno stanje bolesnika te etiologija i opseg primarne ozljede. Znatniji oporavak događa se u prvih 6 mjeseci nakon nastupa deficita. Spontani oporavak od afazije je najuspješniji tijekom prva 3 mjeseca, ali se poboljšanja mogu dogoditi čak i kasnije. Učestalost potpunog oporavka kreće se od 21% do 50%. Afazije kod traumatskih slučajeva oporavljaju se brže od vaskularnih. Unatoč brojnoj literaturi o procjeni i liječenju afazije, tek je vrlo malo napisano o samom završetku terapije. Naša saznanja stečena iskustvom kazuju da logopedska terapija treba trajati sve dotle dok se postiže uspjeh u oporavku početnih smetnji (1 do 3 godine) i dok je bolesnik motiviran. Uočeno je da nakon završetka kontinuiranog logopedskog tretmana dolazi do stagnacije ili regresije oporavljenih smetnji, te se bolesnici nakon jedne godine od završetka logopedske terapije ponovno javljaju logopedu.

## QUALITY OF LIFE AND REHABILITATION IN COMMUNITY – LIVING WITH STROKE

### KVALITETA ŽIVOTA I REHABILITACIJA U ZAJEDNICI – ŽIVJETI S MOŽDANIM UDAROM

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Rehabilitation is an integral part of the management of patients with stroke. A key to successful rehabilitation is a coordinated team approach that involves active participation by several rehabilitation specialists who can provide services to patients on a case-by-case basis. Rehabilitation should begin as soon as the patient is medically stable. Early treatment, continuing encouragement and orientation towards the outside environment are important. Education of the patient and his family about stroke and its consequences is an important step in rehabilitation. Family members should be informed about the neurologic impairment.

Most patients will need evaluation and treatment by a physical therapist, a speech pathologist, and an occupational therapist. In some cases, vocational rehabilitation specialists, recreation therapists or neuropsychologist/cognitive rehabilitation specialist will be needed. The involvement of the nursing service also is critical. These professionals should assess patients and tailor treatment plan to each individual patient's needs. Plans should respect the wishes of the patient and his family as well as the patient's neurologic and general medical status. Each rehabilitation service specializes in different aspects of the patient's recovery.

Physical therapy concentrates on the following aspects: mobilization, walking, major motor or sensory impairment of the limbs and prescription of devices, such as a cane or walker. Speech pathology addresses the following issues: disorders of language, disorders of articulation and disorders of swallowing. Occupational therapy focuses on the following issues: fine movements of the hand, arm function, utilization of tools and assistive devices, and ability to function independently. Occupational and physical therapy should emphasize using affected limbs and achieving

Rehabilitacija je sastavni dio liječenja bolesnika s moždanim udarom (MU). Za uspješnu rehabilitaciju ključan je usklađeni timski pristup koji uključuje djelatno sudjelovanje nekoliko specijalista u rehabilitaciji koji bolesniku mogu pružiti skrb strogo utemeljenu na svakom pojedinačnom slučaju. S rehabilitacijom treba započeti čim je bolesnik u medicinski stabilnom stanju. Važno je rano liječenje, stalno ohrabivanje i orijentacija prema vanjskoj okolini. Obrazovanje bolesnika i njegove obitelji o MU i njegovim posljedicama važan je korak u rehabilitaciji. Članove obitelji treba obavijestiti o neurološkom poremećaju. U većine je bolesnika potrebna procjena i liječenje fizioterapeuta, logopeda i radnog terapeuta. U nekim slučajevima potrebne su usluge neuropsihologa/specijalista za kognitivnu rehabilitaciju. Veoma je važna i sestrińska usluga. Svi ovi stručnjaci trebaju procijeniti bolesnika i planirati liječenje na temelju potreba svakog pojedinog bolesnika. Pritom treba u obzir uzeti želje bolesnika i njegove obitelji, kao i bolesnikov neurološki i opće medicinski status. Svaka je rehabilitacijska služba specijalizirana za različite vidove bolesnikova oporavka. Fizikalna terapija usredotočena je na sljedeće aspekte: mobiliziranje, hodanje, veći motorički ili senzorni poremećaj ekstremiteta i propisivanje pomagala kao što je štap ili uređaj za pomoć pri hodaњу. Patologija govora usmjerena je na sljedeća pitanja: jezične poremećaje, poremećaje artikulacije i poremećaje gutanja. Radna terapija upućena je na sljedeća pitanja: fini pokreti šake i ruke, uporaba sredstava za rad i pomagala, te sposobnost neovisnog funkcioniranja. U radnoj i fizikalnoj terapiji naglasak treba biti na upotrebi zahvaćenih ekstremiteta i postizanju spretnosti pri jelu, oblačenju, osobnoj higijeni i drugim osnovnim potrebama. Dok uvodni koraci u rehabilitaciji počinju u okruženju akutne skrbi, valja načiniti plan za neprekidnu bolničku i

proficiency in eating, dressing, toilet functions, and other basic needs.

While the preliminary steps in rehabilitation begin in an acute-care setting, a plan should be developed for continued inpatient and outpatient rehabilitation.

New interventions to help motor recovery after stroke include constraint-induced movement therapy and medications to control spasticity. Promising therapies include robot training, electrical stimulation, magnetic field therapy, intermittent compression and intensive physical therapy.

Patients should be assessed at regular intervals during their recovery from stroke. The types and settings of rehabilitation are adjusted in response to the patient's responses and condition. The goal will be for the individual to be as independent as possible.

Depression is common following stroke. The mood disorder can be an emotional response to the sudden and devastating change in the patient's life and independence. Depression after stroke is also an organic consequence of the brain injury. They should be expected and treated by reassurance and understanding. Emotional disturbances can hamper recovery from stroke and limit the efficacy of rehabilitation. Often, counseling and use of antidepressants are needed.

Younger age, limited sensory and motor deficit, intact mental function and a helpful home environment favorably influence rehabilitation. The patient, relatives and friends must understand the nature of the disabilities and the likelihood that improvement can occur, but only with time, patience and perseverance. The ultimate goal of the rehabilitation should be to provide continued long-term medical treatment and rehabilitation that meet the patient's and family's wishes and needs.

izvanbolničku rehabilitaciju. Novi postupci za pomoć u oporavku nakon MU uključuju terapiju pokretima izazvanim ograničenjima te lijekove za kontrolu spasticiteta. Vježbanje pomoću robota, električna stimulacija, terapija pomoću magnetskog polja, naizmjenična kompresija te intenzivna fizikalna terapija vrste su liječenja koje obećavaju. Procjenu bolesnika treba provoditi u redovnim vremenskim razmacima tijekom oporavka od MU. Vrste i okruženja rehabilitacije prilagođavaju se prema bolesnikovu odgovoru i stanju. Cilj je u svakog pojedinca postići najveću moguću razinu neovisnosti. Depresija je česta nakon MU. Poremećaj raspoloženja može biti emocionalni odgovor na iznenadnu i pogubnu promjenu u bolesnikovu životu i neovisnosti. Depresija nakon MU nastaje i kao organska posljedica moždane ozljede. Takve poremećaje treba očekivati i liječiti ih razuvjeravanjem i razumijevanjem. Emocionalni poremećaji mogu usporiti oporavak od MU i ograničiti učinkovitost rehabilitacije. Često je potrebno savjetovanje i primjena antidepressiva. Na rehabilitaciju povoljno utječu mlađa životna dob, ograničen senzorni i motorički deficit, neporemećena mentalna funkcija i susretljiva kućna okolina. Bolesnik, njegova rodbina i prijatelji moraju shvatiti narav onemoćalosti i vjerojatnost da je poboljšanje moguće, ali tek s vremenom, uza strpljenje i ustrajnost. Konačan cilj rehabilitacije treba biti osiguranje neprekidnog dugotrajnog medicinskog liječenja i rehabilitacije koji će ispuniti želje i potrebe bolesnika i njegove obitelji.

## EPIDEMIOLOGIC AND ECONOMIC PARAMETERS OF CEREBROVASCULAR DISEASE IN CROATIA

## EPIDEMIOLOŠKI I GOSPODARSKI POKAZATELJI CEREBROVASKULARNE BOLESTI U HRVATSKOJ

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The second half of the twentieth century was characterized by a significant increase in the prevalence of chronic noncontagious diseases in all industrialized countries of the world, which stimulated many epidemiologic studies that showed a high mortality rate for vascular diseases. The highest mortality rates were recorded in the countries of central and east Europe (Estonia 1401, Lithuania 1405, and Ukraine 1490 *per* 100,000), and lowest in France, Spain and Switzerland (330, 399, and 477/100,000, respectively). Over the last decade, the leading cause of death in Croatia were cerebrovascular diseases. In Croatia, the standardized mortality rate at age 0-64 in 1999 was 30.64/100,000, whereas in Austria and Slovenia it was 10.15/100,000 and 16.65/100,000, respectively. The standardized rate of all deaths from cerebrovascular diseases was also found to be on an increase and was 186.65/100,000 in 1999, as compared to 73.48/100,000 in Austria and 92.01/100,000 in Slovenia. Considering the increasing trend of deaths attributed to cerebrovascular morbidity in recent years in Croatia, whereas a decrease has been recorded in other countries owing to successful prevention and early diagnosis, we tried to calculate objective costs that include, in addition to the cost of treatment, work inability, rehabilitation, and economic losses. On the assessment of non-medical costs, we followed the current measures used by insurance companies according to the mean life expectancy.

According to epidemiologic data of the National Institute of Public Health, 8175 patients of both sexes, 1342 (16.41%) of them in the productive age <65, died during 1999 from cerebrovascular diseases. The costs of their treatment were 81,227,580 HRK, and losses from premature death 202,631,000 HRK. Upon calculating (evaluating) all costs except for the standard cost of treatment at all health care levels, the costs due to life expectancy reduction as compared with the mean life expectancy for Croatia in 1999 were assessed.

Druga polovica dvadesetoga stoljeća obilježena je značajnim porastom kroničnih nezaraznih bolesti u svim razvijenim zemljama svijeta, što je potaklo brojne epidemiološke studije koje su pokazale visoku stopu mortaliteta oboljelih od bolesti krvožilnog sustava. Stopa smrtnosti bila je najviša u zemljama središnje i istočne Europe (Estoniji 1.401, Latviji 1.405 i Ukrajini 1.490/100.000 stanovnika), a najniže stope zabilježene su u Francuskoj, Španjolskoj i Švicarskoj (330, 399 odnosno 477/100.000 stanovnika). Vodeći uzrok smrti posljednjega desetljeća u Hrvatskoj su cerebrovaskularne bolesti. Standardizirana stopa umrlih u dobi od 0-64 godine života za 1999. g. je 30,64/100.000 stanovnika, dok je za isto razdoblje u Austriji 10,15, a u Sloveniji 16,65. U porastu je standardizirana stopa smrtnosti svih umrlih od cerebrovaskularnih bolesti, pa je 1999. g. 186,65/100.000 stanovnika, dok je u Austriji 73,48, a u Sloveniji 92,01/100.000 stanovnika. S obzirom na porast broja umrlih posljednjih godina u nas, dok druge zemlje bilježe smanjenje provođenjem uspješne prevencije i rane dijagnostike, pokušali smo izračunati objektivne troškove koji uz troškove liječenja uključuju radnu nesposobnost, rehabilitaciju i gubitke u gospodarstvu. U procjeni nemedicinskih troškova vodili smo se važećim mjerilima osiguravajućih društava prema prosječnoj očekivanoj dobi života. Na temelju epidemioloških podataka Hrvatskoga zavoda za javno zdravstvo tijekom 1999. godine umrlo je od cerebrovaskularnih bolesti 8.175 osoba oba spola. Prema tim podatcima 1.342 (16,41%) umrle osobe bile su u produktivnoj dobi do 65 godina života. Troškovi njihovog liječenja iznosili su 81.227.580 kn, a gubitci zbog prerane smrti bili su 202.631.000 kn. Pri izračunu (procjeni) svih troškova osim standardnih troškova liječenja u svim razinama zdravstvene zaštite izvršili smo procjenu troškova nastalih zbog skraćivanja životne dobi prema prosjecima očekivane životne dobi u 1999.g. za Hrvatsku. Tijekom 2000. godine u primarnoj zdravstvenoj zaštiti liječeno je 42.111 oboljelih od cerebrovaskularnih bolesti, od kojih je



During 2000, 42111 patients with cerebrovascular diseases were treated at primary health care; 18,003 of them were hospitalized, and 8382 patients died. The cost of treatment for cerebrovascular diseases was 1,450,623,897 HRK or 11.107% of total health insurance expenditure in 2000. As cerebrovascular diseases occur as a consequence of risk factors, the costs of simultaneous treatment of other chronic noncontagious diseases could not be singled out.

The morbidity and mortality of cerebrovascular diseases could be relatively quickly reduced by gradual but steady investment in the prevention and rapid diagnosis and management of acute states. The invested resources would be returned soon, while the present costs would be significantly reduced (by 30% - 40%), and direct savings for the economic system would be realized, eventually resulting in an increase of the gross national product.

18.003 bolesnika bolnički liječeno, dok su 8.382 bolesnika preminula. Tijekom 2000. godine troškovi liječenja od cerebrovaskularnih bolesti iznosili su 1.450.623.897 kn ili 11,107% sveukupnih troškova zdravstvenog osiguranja za 2000. godinu. S obzirom na to da su cerebrovaskularne bolesti posljedica rizičnih čimbenika, u troškovima liječenja nije bilo moguće isključiti troškove istodobnog liječenja i drugih kroničnih nezaraznih bolesti. Postupnim investiranjem u prevenciju i brzu dijagnostiku i liječenje akutnih stanja moglo bi se relativno brzo smanjiti pobol i smrtnost od cerebrovaskularnih bolesti. Uložena sredstva brzo bi se povratila, dok bi se postojeći troškovi značajno smanjili (za 30% do 40%) i ostvarile izravne uštede gospodarskom sustavu u cilju rasta bruto društvenog proizvoda.