Primjena farmakoinvazivne strategije u mreži primarne perkutane koronarne intervencije zapadne Slavonije

Application of pharmacoinvasive strategy in primary percutaneous coronary intervention network in Western Slavonia

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SAŽETAK: Hrvatska mreža primarne perkutane intervencije međunarodno je prepoznati sustav dobre organizacije urgentnog liječenja kardioloških bolesnika. U svakodnevnoj kliničkoj praksi svjedoci smo da je vrijeme potrebno za organiziranje primarne perkutane koronarne intervencije (pPCI), koja predstavlja najbolji način reperfuzijske terapije u liječenju bolesnika s akutnim infarktom s elevacijom ST-segmenta, često predugo i povezano s neprihvatljivo dugim kašnjenjima.

Farmakoinvazivna strategija obuhvaća selektivnu primjenu fibrinolitičke terapije nakon koje slijedi neodložan transport bolesnika u centar s mogućnošću perkutane koronarne intervencije i organiziranje invazivne obrade unutar 3-24 sata. Obzirom na organizacijske teškoće koje uzrokuju nemogućnost pravovremene pPCI, primjenom farmakoinvazivnog pristupa povećao bi se broj bolesnika kojima bi bila omogućena pravilna i pravodobna reperfuzijska terapija.

Donosimo praktične preporuke za implementaciju farmakoinvazivne strategije u svakodnevnu kliničku praksu te protokol lokalne organizacije mreže pPCI u Općoj bolnici "Dr. Josip Benčević" u Slavonskom Brodu, Hrvatska.

KLJUČNE RIJEČI: infarkt miokarda, farmakoinvazivna strategija, fibrinolitička terapija, primarna perkutana koronarna intervencija, mreža primarne perkutane intervencije

SUMMARY: Croatian Primary Percutaneous Intervention Network is an internationally recognized system of good organization of urgent treatment of cardiac patients. In everyday clinical practice, we have witnessed that the time required for the organization of primary percutaneous coronary intervention (pPCI), which represents the best way of reperfusion therapy in the treatment of patients with acute ST-segment elevation myocardial infarction is often too long and associated with unacceptably long delays.

Pharmacoinvasive strategy encompasses a selective use of fibrinolytic therapy to be followed by prompt transportation of patients to a center capable of undertaking percutanous coronary intervention and organizing invasive treatment within 3-24 hours. Considering the organizational difficulties caused by the incapability of undertaking prompt pPCI, the application of pharmacoinvasive approach would increase the number of patients that would be provided proper and timely reperfusion therapy.

Here are some practical recommendations for implementation of the pharmacoinvasive strategy in everyday clinical practice and protocol of the local organization of the pPCI network in the General Hospital "Dr. Josip Benčević" in Slavonski Brod, Croatia.

KEYWORDS: myocardial infarction, pharmacoinvasive strategy, fibrinolytic therapy, primary percutaneous coronary intervention, primary percutaneous coronary intervention network.

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Prikaz slučaja

Muškarac u dobi od 60 godina dolazi vlastitim prijevozom u Hitni prijem Opće županijske bolnice Požega u 17 sati radi bolova u prsima intenziteta 8/10 koji traju unazad 40 minuta. Vitalni znaci su stabilni. U 12-kanalnom EKG-u snimljenom i interpretiranom unutar pet minuta od dolaska registrira se elevacija spojnice za 3-4mm u odvodima V1-V4.

Pitanja koja si postavlja dežurni liječnik:

Case report

A man aged 60 comes to the emergency room of the County General Hospital Požega by his own transportation vehicle at 17 hours complaining of chest pains of intensity 8/10, lasting for 40 minutes. Vital signs are stable. The 12-lead ECG recorded and interpreted within five minutes since the arrival registers segment elevation by 3-4 mm in leads V1-V4.

The questions posed by the physician:

• Trebam li bolesnika primiti u koronarnu jedinicu i ordinirati mu fibrinolitičku terapiju? Do početka ordiniranja alteplaze proći će dodatnih 15 minuta.

• Trebam li organizirati prijevoz bolesnika u kateterizacijski laboratorij u bolnici u Slavonskom Brodu? Do dolaska kola hitne medicinske pomoći proći će još 20 minuta, prijevoz do 43 km udaljenog Slavonskog Broda trajat će oko 45 minuta, a bolesnik će biti primljen direktno u kateterizacijski laborator gdje će ga čekati spremna ekipa za primarnu perkutanu koronarnu intervenciju (pPCI) i njima će trebati oko 30 minuta da žicom prođu okluziju u koronarnoj arteriji.

Hrvatska mreža primarne perkutane koronarne intervencije

Najviša kvaliteta skrbi u liječenju bolesnika s akutnim infarktom s elevacijom ST-segmenta (STEMI) znači pružanje homogene, pravodobne, učinkovite i sigurne reperfuzijske terapije najvećem dijelu pacijenata. Ovakve ciljeve može postići samo odlično organizirana lokalna mreža koja uključuje multidisciplinarni timski pristup s jedinstvenim jasno definiranim standardiziranim protokolom, uz kontinuiran nadzor kontrole kvalitete monitoriranjem vremena kašnjenja i kliničkih ishoda.

Hrvatska mreža pPCI trenutno pokriva oko 70% državnog teritorija[1], naša zemlja zauzima visoko peto mjesto u Europi s oko 85% bolesnika sa STEMI koji su reperfundirani[2] (70% pPCI, 15% fibrinolitičkom terapijom), a broj liječenih bolesnika se povećava svake godine. U Hrvatskoj su tijekom 2012. godine učinjena 2,222 postupaka pPCI[3] što je gotovo 500 pPCI na 1 milijun stanovnika i približavamo se cilju inicijative "Stent for life" Europskog kardiološkog društva od najmanje 600 pPCI na milijun stanovnika. *Babić i sur*[4] su nedavno prikazali razvoj Hrvatske mreže pPCI. Stalni je godišnji porast bolesnika sa STEMI liječenih pomoću pPCI, liječe se bolesnici sa sve težim kliničkim profilom, a vrijeme potrebno za izvođenje pPCI od trenutka prezentacije je sve kraće te u posljednje tri godine prosječno iznosi 106 minuta. Svi ovi podaci dokazuju da je Hrvatska mreža pPCI dobro organiziran sustav skrbi urgentnog liječenja kardioloških bolesnika. Hrvatska kardiologija uspješno prati i sve suvremene trendove u intervencijskoj kardiologiji u svijetu[5]. Uprkos svim ovim činjenicama, jedan od primarnih zadataka intervencijskih kardiologa je dalje unaprijeđenje nacionalne mreže pPCI.

Mnogo je značajki koje su istaknute kao važne u organiziranju regionalnih mreža pPCI[6]. Najvažnije među njima su uključivanje adekvatno opremljenog i educiranog sustava hitne medicinske pomoći u prehospitalnu dijagnozu, trijažu i početno liječenje, telekonzultacija s referentnim invazivnim kardiološkim centrom, jasan pisani destinacijski protokol s preciznim definiranjem zemljopisnih područja odgovornosti za centre s mogućnošću pPCI, aktiviranje intervencijskog centra jednim telefonskim pozivom, dolazak tima za pPCI unutar 20 minuta od poziva, kod dolaska bolesnika u intervencijski centar prijem bolesnika sa STEMI direktno u kateterizacijski laboratorij (zaobilazeći jedinice hitnog prijema ili koronarne jedinice), pPCI centri trebaju pružati 24 sata dnevno/7 dana u tjednu te biti sposobni učiniti pPCI unutar 60 minuta od prijema bolesnika sa STEMI. Izrazito je važno naglasiti da pPCI zahtjeva mnoge kliničke, kognitivne i proceduralne vještine te da postoji povezanost između iskustva (broj učinjenih procedura i ustanove i svakog opteratora pojedinačno) i ishoda. Američke smjernice iz 2011. god. preporučuju minimum od 11 pPCI po operatoru te 36 pPCI procedura za ustanovu godišnje[7]. Posljednje američke preporuke

Croatian Primary Percutaneous Coronary Intervention Network

• Do I need to refer the patient to the coronary care unit and administer fibrinolytic therapy to him? It will take additional 15 minutes till the start of administering alteplase.

• Do I need to arrange the transportation of the patient to the catheterization lab at the hospital in Slavonski Brod? It will take another 20 minutes for the ambulance to arrive, the transportation will last for 45 minutes considering the distance of up to 43 km to get to Slavonski Brod and the patient will be admitted directly to the catheterization laboratory where the team will be prepared for primary percutaneous coronary intervention (pPCI) and it will take them about 30 minutes to get the guide wire through the occlusion in the coronary artery.

The highest quality of the treatment of patients with acute ST-segment elevation myocardial infarction (STEMI) means providing a uniform, timely, efficient and safe reperfusion therapy to the greatest number part of patients. These goals can only be achieved by well organized local network that includes a multidisciplinary team approach with a single well-defined standardized protocol, with a continuous monitoring of quality control by monitoring the time deleys and clinical outcomes.

The Croatian pPCI Network currently covers around 70% of the state territory[1], our country is ranked the high fifth with around 85% of patients with STEMI who are reperfused[2] (70% by pPCI, 15% by fibrinolytic therapy), whereas the number of treated patients increases every year. In Croatia during the year 2012, some 2.222 pPCI procedures[3] were performed which is almost 500 pPCI in 1 million of inhabitants and we are getting closer to the goal set by the initiative "Stent for life" of the European Society of Cardiology of at least 600 pPCI in one million inhabitants. *Babić et al*[4] have recently presented the development of the Croatian pPCI network. There is an increasing number of patients with STEMI treated by pPCI on an annual basis, the patients with more severe clinical profile are treated and the time required to perform pPCI from the moment of presentation is shorter and shorter, and in the last three years the median time is 106 minutes. All these data show that the Croatian pPCI Network is a well-organized system of care for urgent treatment of cardiac patients. Croatian cardiology successfully monitors all modern trends in interventional cardiology in the world[5]. Despite all these facts, one of the primary tasks of interventional cardiologists is still improving the national pPCI network.

There are many characteristics that are emphasized as significant ones in organizing regional pPCI networks.[6] The most important among them is the involvement of an adequately equipped and trained system of emergency medical services into the prehospital diagnosis, triage and initial treatment, teleconsultation with reference invasive cardiology center, a clear written destination protocol with a precise definition of the geographical areas of responsibility for the centers capable of performing pPCI, activating intervention center by one phone call, the arrival of the pPCI team within 20 minutes from the call, in case of arrival of the patients to the intervention center, the admission of patients with STEMI directly to the catheterization lab (avoiding emergency admission units or coronary units), pPCI centers should provide the 24/7 service and be capable of performing pPCI within 60 minutes from the admission of patients with STEMI. It is particularly important to emphasize that pPCI requi-

navode da je volumen ustanove <200 ukupnih perkutanih koronarnih intervencija (PCI) godišnje (i elektivnih i primarnih) predstavlja prag minimalno učinjenih procedura koji je povezan s lošijim kliničkim ishodima, a da iznad ovog broja ne postoji povezanost višeg godišnjeg volumena i boljih kliničkih ishoda[8]. Preporuka je da svaki operator pojedinačno treba izvesti minimalno 50 PCI procedura godišnje za održavanje kompetentnosti.

U nedostatku kompletnog zajedničkog registra koji bi nam omogućio monitoriranje i poboljšanje svake od navedenih komponenti teško je reći kako se najefikasnije može podići kvalitetu skrbi za bolesnike sa STEMI unutar Hrvatske mreže pPCI. Čak i u idealno oraniziranoj mreži pPCI neće biti moguće svim bolesnicima sa STEMI organizirati liječenje pPCI u vremenskim okvirima koje nam zadaju smjernice. Jedan od načina poboljšanja kvalitete mreže je i primjena farmakoinvazivnog pristupa.

Pozicija farmakoinvazivne strategije u mreži primarne perkutane koronarne intervencije

1. Kojeg bolesnika sa STEMI trebam uputiti na pPCI, a kojeg liječiti farmakoinvazivnim pristupom?

a) jednostavniji odgovor: o načinu reperfuzije odlučujemo samo na osnovu vremena proteklog od početka simptoma i na osnovu očekivanog vremena kašnjenja pPCI.

Za bolesnike koji se prezentiraju nakon 3 sata iza početka bolova i ukoliko od početka tegoba pa do predmnijevanog dolaska u tercijarni centar nije prošlo više od 12 sati, pPCI je metoda izbora u svakom slučaju. Za bolesnike koji dolaze u bolnicu koja ima mogućnost izvođenja pPCI odgovor je jednostavan — pPCI je metoda izbora ako se reperfuzija pPCI može organizirati unutar 60 minuta od prvog kontakta sa sustavom organizirane medicinske skrbi (FMC, first medical contact). Za bolesnike koji se prezentiraju unutar tri sata od početka bolova na mjestu gdje liječenje pPCI nije izvodivo (bolnica bez mogućnosti liječenja pPCI, ali i na drugim mjestima ulaska u medicinski sustav, npr. na terenu gdje je pozvana hitna medicinska pomoć) odluka je kompleksnija. Ukoliko procijenimo da nam treba manje od dva sata do postizanja reperfuzije, metoda pPCI je i dalje terapija izbora. Pri tome treba imati u vidu da se vremenom reperfuzije smatra početak trombolize ili vrijeme prolaska žice vodilje kroz leziju odgovornu za STEMI. Dakle, liječnik koji donosi odluku treba uzeti u obzir 3 vremenska razdoblja: vrijeme potrebno za započinjanje fibrinolitičke terapije, vrijeme transporta te vrijeme od ulaska u bolnicu koja ima mogućnost liječenja pPCI do prolaska žice kroz odgovornu leziju. Sva navedena vremena su indikatori dobre organizacije i kvalitete skrbi za bolesnike sa STEMI, a različita su za svaku pojedinu ustanovu i za svaku pojedinu regiju.

b) kompliciraniji odgovor: odluka o vrsti reperfuzijske terapije se donosi ne samo na osnovu vremena proteklog od početka simptoma i na osnovu očekivanog vremena kašnjenja pPCI, nego će ju modulirati i kliničke karakteristike bolesnika.

Logično je za pretpostaviti da kod izbora reperfuzijske terapije treba voditi računa i o osnovnim kliničkim karakteristikama bolesnika sa STEMI. Poradi razvoja tromborezistencije efikasnost fibrinolitičke terapije je to manja što se bolesnik javi kasnije od početka simptoma[9] (i obrnuto). Što je bolesnik mlađi, veća je sigurnost fibrinolitičke terapije, i obrnuto, rizik krvarenja je veći u starijih bolesnika, pogotovo rizik od životno ugrožavajućih intrakranijskih krverenja[10].

res many clinical, cognitive and procedural skills and that there is a link between experience (a number of procedures performed both by an institution and every operator individually) and the outcome. The 2011 American Guidelines recommend a minimum of 11 pPCI per operator and 36 pPCI procedures per institution on an annual basis[7]. The most recent American guidelines mention that the volume of an institution of <200 total percutaneous coronary interventions (PCI) a year (both elective and primary ones) is the threshold of minimum performed procedures associated with poor clinical outcomes, while a higher number than that shows that there is no link between a higher annual volume and better clinical outcomes[8]. The recommendation is that every operator individually should perform a minimum 50 PCI procedures a year to maintain his/her competence.

In the absence of complete joint registry that would enable us monitoring and improvement of each of these components, it is difficult to say how efficiently we can improve the quality of management of patients with STEMI within the Croatian pPCI Network. Even in ideally organized pPCI network, it will not be possible to organize the pPCI treatment for all patients with STEMI within the timeframe set by the guidelines. One of the ways to improve the quality of network is to apply pharmacoinvasive approach.

The position of the pharmacoinvasive strategy in the primary percutaneous coronary intervention network

1. What patient with STEMI is to be referred to pPCI and what patient is to be treated by pharmacoinvasive approach?

a) A simple answer: we decide on the manner of reperfusion only on the basis of the time elapsed from the onset of symptoms and on the basis of the expected pPCI delay time.

For patients who present after 3 hours after the onset of pains, and if no more than 12 hours have elapsed from the onset of symptoms till the arrival at the tertiary center, pPCI is the method of choice in any case. For patients who come to the hospital that is capable of performing pPCI the answer is simple — pPCI is the method of choice if reperfusion pPCI can be organized within 60 minutes from the first medical contact (FMC). For patients who are presented within three hours from the onset of pains at the site where the treatment with pPCI is not feasible (the hospital without pPCI treatment options, but also at other sites of entry into the medical system, for example, in the field where the emergency medical service is invited) the decision is more complex. If we assess that is takes less than two hours to the performance of reperfusion, the pPCI method is still the treatment of choice. It should be borne in mind that the time of reperfusion is considered the start of thrombolysis or the time of passage of the guide wire through the lesion responsible for STEMI. Therefore, the physician who makes the decision needs to take into account the three time periods: the time required for initiation of fibrinolytic therapy, the time of transportation and the time of entry into the hospital capable of treating pPCI till the passage of the guide wire through the responsible lesion. All the times are the indicators of good organization and quality of care for patients with STEMI, and are different for each institution and for each particular region.

b) More complicated answer: decision on the type of reperfusion therapy is made not only based on the time elapsed from the onset of symptoms and on the basis of the expected pPCI time delay, but it will be modulated by the clinical characteristics of patients.

Važnost uspješne reperfuzije je to važnija što je veća masa miokarda ugrožena (brzina reperfuzije je važnija kod infarkta prednje stijenke nego u ostalim lokalizacijama).

Pinto i sur[11] su analizirali podatke o čak 192.509 bolesnika liječenih od lipnja 1994. do kolovoza 2003. godine u 645 bolnica u Sjedinjenim Američkim Državama. Za svaku bolnicu su izračunali kašnjenje koje je nastupilo radi organiziranja pPCI ("PCI-related delay") tako da su od vremena koje je proteklo od FMC do inflacije balona u pPCI ("door-to-balloon" time) oduzimali vrijeme proteklo od FMC do započinjanja fibrinolitičke terapije ("door-to-needle"time). "PCI-related delay" dakle predstavlja teoretski vremenski interval između vremena kada je bolesnik mogao primiti fibrinolitičku terapiju i vremena kada je mogao imati napuhan balon u okludiranoj krvnoj žili. Autori su potom statističkim modelima odredili povezanost između "PCI-related delay", izabrane vrste reperfuzijske terapije i karakteristika bolesnika (dob, lokalizacija infarkta, vrijeme proteklo od početka simptoma) i njihovu povezanost s bolničkim mortalitetom. Na taj način su odredili vremensku granicu kašnjenja pPCI ("PCI-related delay") nakon koje se gubi prednost pPCI u odnosu na fibrinolitičku terapiju, drugim riječima koliko smijemo izgubiti vremena za organiziranje pPCI da bi primjena ove metode reperfuzije dovela do manjeg hospitalnog mortaliteta nego da smo primijenili fibrinolitičku terapiju. Najkraća "ravnoteža mortaliteta" (manja od 1 sat) je registrirana u bolesnika mlađih od 65 godina, koji su se prezentirali unutar 2 sata od nastanka tegoba, a najdulja (gotovo 3 sata) kod bolesnika starijih od 65 godina sa infartom bilo koje druge lokalizacije od prednje, koji su se prezentirali više od 2 sata od početka tegoba. Ovi podaci jasno pokazuju da kliničke karakteristike bolesnika (dob, trajanje simptoma i lokalizacija infarkta) značajno utječu koliko brzo se gubi prednost pPCI u odnosu na fibrinolitičku terapiju. **Tablica 1** predstavlja podatke iz članka Pinto i sur[11] na način da liječnicima koji rade u uvjetima gdje pPCI nije odmah dostupna olakša često tešku odluku da li primijeniti fibrinolitičku terapiju ili bolesnika transportirati radi liječenja pPCI.

It is logical to assume that in case of selection of reperfusion therapy we should take into account the basic clinical characteristics of patients with STEMI. Due to the development of thromboresistance, the efficacy of fibrinolytic therapy is lower if the patient arrives later after the onset of symptoms[9] (and vice versa). The younger a patient is, the greater safety of fibrinolytic therapy it will be, and vice versa, the risk of bleeding is increased in elderly patients, especially the risk of life-threatening intracranial hemorrhage[10]. The importance of successful reperfusion is more important if the greater mass of myocardium is impaired (the speed of reperfusion is more important in anterior wall infarction than in other localizations).

Pinto et al[11] analyzed the data on even 192,509 patients treated from June 1994 to August 2003 in 645 hospitals in the United States of America. They calculated the PCI related delay for each hospital, so from the door-to-balloon time they deducted door-to-needle time. "PCI-related delay" theoretically represents the time interval between the time when a patient could have received fibrinolytic therapy and the time when he could have had inflated balloon in the occluded blood vessel. The authors have later used statistical models to determine the association between "PCI-related delay", the selected type of reperfusion therapy and patient's characteristics (age, localization of infarction, time from the onset of symptoms) and their association with hospital mortality. In this way, they set the time limit for PCI-related delay after which pPCI loses advantage over the fibrinolytic therapy, in other words, how much time we are allowed to lose to organize pPCI so that the use of this method of reperfusion would lead to lower hospital mortality than if we had used fibrinolytic therapy. The shortest "mortality balance" (less than 1 hour) is registered in patients younger than 65 years, who were presented within two hours from the onset of symptoms, and the longest one (almost three hours) in patients over 65 years of age with infarction of any other localization but the anterior one, who were presented after 2 hours from the onset of symptoms. These data clearly show that the clinical features of patients (age, length of symptoms, localization of myocardial infarction) greatly affect on how fast pPCI loses advantage over fibrinolytic therapy. **Table 1** presents the data from the articles of Pinto et al[11] in the way make it easier for physicians who work in the conditions where pPCI is not immediately available to make a hard decision on whether to apply fibrinolytic therapy or transport the patients for pPCI treatment.

Age	<65 years				>65 years			
Localization of myocardial infarction on ECG	anterior		nonanterior		anterior		nonanterior	
Symptom onset to first medical contact time	<120 min	>120 min	<120 min	>120 min	<120 min	>120 min	<120 min	>120 min
„PCI related delay" where PCI and fibrinolytic mortality are equal (min)	40	43	58	103	107	148	168	170

PCI = percutaneous coronary intervention; min = minutes.

Table 1. *Relationship of prehospital delay, age, and infarct location to the loss of PCI-related mortality benefit*

Treba naglasiti da će najteži bolesnici sa STEMI imati najveću korist od pPCI, dakle bolesnici sa slikom kardiogenog šoka, srčanog popuštanja, hemodinamski ili aritmološki nestabilni bolesnici. U ovoj grupi bolesnika treba lakše

It should be emphasized that the highest risk patients with STEMI will mostly benefit from pPCI, that is, the patients with a diagnosis of cardiogenic shock, heart failure, or hemodynamically or arrhythmically unstable patients. The

donijeti odluku da pPCI bude terapija izbora u odnosu na fibrinolitičku terapiju.

2. Da li svakog bolesnika kojem sam ordinirao fibrinolitičku terapiju trebam uputiti na invazivnu obradu?

U protokolima studija o farmakoinvazivnom pristupu koji su prikazani u članku u ovom broju časopisa[12] može se primijetiti da je već i u studijama dizajniranim prije desetak godina veliki dio bolesnika unutar iste hospitalizacije invazivno obrađen i revaskulariziran, dok je taj broj u novijim studijama izrazito visok. U TRANSFER AMI[13] koronarografirano je 89% bolesnika liječenih fibrinolizom, 93% u NORDISTEMI[14], a u STREAM[15] istraživanju su svi bolesnici invazivno obrađeni. Možemo reći su ova istraživanja odgovarala na pitanje da li je indicirana rana ili odgođena invazivna obrada, a ne da li je indiciran rutinski ili selektivni invazivni pristup nakon fibrinolitičke terapije. Čini se da je odgovor na gore navedeno pitanje jednostavan i on se može naći u najnovijim smjernicama. Europske smjernice[16] predlažu rutinsku invazivnu obradu svim bolesnicima koji su liječeni fibrinolitičkom terapijom neovisno o uspjehu fibrinolitičke terapije (Klasa IA), kao i američke smjernice[17] koje takođe preporučuju rutinsku koronarografiju svih bolesnika koji su liječeni fibrinolizom, s time da se bolesnicima u kardijalnom šoku te s teškim akutnim popuštanjem preporuča urgentna invazivna obrada (klasa I preporuka), a za sve ostale bolesnike liječene fibrinolitičkom terapijom rutinska koronarografija ima preporuku klase IIa, s preporukom da se učiniti što je prije moguće, idealno unutar 24 sata, ali ne unutar 2 do 3 sata nakon od primjene fibrinolitičke terapije.

3. Kada bolesnike liječene fibrinolitičkom terapijom trebam uputiti invazivnom kardiologu? Koliki je rizik komplikacija za vrijeme transporta?

Odgovor o vremenu transporta naveden je u smjernicama: invazivnu obradu treba učini 3-24 sata nakon fibrinolize. Randomizirana kontrolirana ispitivanja su evaluirala rutinsku u odnosu na selektivnu invazivnu obradu (ranija istraživanja), ili ranu o odnosu na kasnu invazivnu strategiju (novije studije) i vremena unutar kojih je invazivna obrada učinjena u grupi ispitanika liječenih farmakoinvazivnom strategijom su varirala od 84 min (CAPITAL AMI[18]) do 16,7 sati (GRACIA[19]), ali u velikoj većini studija invazivna obrada je rađena od 3 do 6 sati nakon započinjanja fibrinolitičke terapije, i čini se da je ovo vrijeme optimalno.

Pitanje sigurnosti transporta bolesnika sa STEMI je takođe jedno od onih koji mogu modulirati odluku o vrsti primijenjene reperfuzijske terapije te o vremenu transporta bolesnika liječenih farmakoinvazivnom strategijom. Niti u jednoj od studija o farmakoinvazivnom pristupu[12] autori ne referiraju smrtne ishode za vrijeme transporta. U studiji TRANSFER AMI[13] 2,4% bolesnika s farmakoinvazivnom strategijom te u 3% u standardno liječenoj skupini je imalo komplikacije tijekom transporta, uglavnom hipotenziju. Postoji više izvješća u medicinskoj literaturi o ovom pitanju. Među 2.258 bolesnika s dijagnozom akutnog koronarnog sindroma ili kardiogenog šoka transportiranih zračnim putem njih 127 (5,6%) je imalo jednu ili više komplikacija[20]. Najčešće se javila hipotenzija, (n=80), pogoršanje bolova u prsnom košu (n=52), i aritmija (n=18), a nije bilo smrtnih ishoda tijekom transporta te autori smatraju da je transport ovih, potencijalno nestabilnih, bolesnika siguran. Isti zaključak donose i *Gachoud i sur*[21] koji nisu imali značajnijih komplikacija tijekom transporta 42 bolesnika radi pPCI. Jedan od 300 bolesnika s bolovima u prsnom košu koji je transportiran privatnim prijevozom je tijekom transporta doživio srčani arest[22]. *Straumann i sur*[23] navod da u grupi od 68 visokorizičnih bolesnika sa

decision is easier to make that pPCI should be the therapy of choice compared to fibrinolytic therapy in this group of patients.

2. Does every patient whom I prescribed fibrinolytic therapy should be referred to invasive treatment?

The protocols of the studies in the pharmacoinvasive approach that are presented in this journal issue[12] show that even in the studies designed ten years ago, a major portion of patients within the same hospitalization underwent invasive treatment and revascularization, while this number is extremely high in the more recent studies. In the TRANSFER AMI[13] 89% of patients treated by fibrinlysis underwent coronarography, 93% of them in the NORDISTEMI[14] trial and in the STREAM[15] trial all the patients underwent the invasive treatment. We can say that trials answered the question as to whether early or delayed invasive treatment was indicated, not whether a routine or selective invasive approach after fibrinolytic therapy was indicated. The answer to the above question seems to be simple and it can easily be found in the most recent guidelines. The European guidelines[16] suggest routine invasive treatment for all patients treated by fibrinolytic therapy regardless of the success of the fibrinolytic therapy (Class IA), as well as the American guidelines[17] that also suggest routine coronarography for all patients treated by fibrinolysis, whereas the patients in cardiac shock and severe acute failure are advised to undergo urgent invasive treatment (class I recommendations), while for all the other patients treated by fibrinolytic therapy, the routine coronarography carries the recommendation class IIa, with the recommendation that it should be done as soon as possible, ideally within 24 hours, but not within 2 to 3 hours after the use of the fibrinolytic therapy.

3. When should I refer the patients treated by fibrinolytic therapy to an invasive cardiologist? What is the risk of complications during the transport?

An answer to the transportation time is specified in the guidelines: invasive treatment should be done 3-24 hours after fibrinolysis. Randomized controlled trials have evaluated the routine in comparison to the selective invasive treatment (previous trials), or early in comparison to late invasive strategy (more recent studies) and time within which an invasive treatment performed in the group of patients treated by pharmacoinvasive strategy varied from 84 min (CAPITAL AMI[18]) to 16,7 hours (GRACIA[19]), but in the vast majority of studies the invasive treatment was performed 3-6 hours after the initiation of fibrinolytic therapy, and this time seems to be optimal.

The issue as to the safety of transportation of patients with STEMI is also one of those that can modulate the decision on the type of reperfusion therapy applied and on the time required to transport patients treated by pharmacoinvasive strategy. In none of these studies on pharmacoinvasive approach[12] the authors do not mention deadly outcomes during the transportation. According to the TRANSFER AMI[13] study 2.4% of patients undergoing pharmacoinvasive therapy and 3% of patients undergoing standard treatment had complications during the transportation, mainly hypotension. There are several reports on this issue in the literature. Among 2,258 patients with diagnosis of acute coronary syndrome or cardiogenic shock transported by air, 127 of them (5.6%) had one or more complications[20]. The most common disorders that occur are hypotension (n=80), impairment of chest pains (n= 52), and arrhythmia (n=18), and there were no deadly incomes during the transport and the authors believe that the transportation of these potentially unstable patients

STEMI, među kojima je njih 17 imalo kardiogeni šok, njih 15 je prije transporta bilo resuscitirano, a 8 tijekom transporta bilo intubirano, niti jedan bolesnik nije umro tijekom transporta koji je trajao 55 (18-115) minuta. *Balenović i sur*[24] navode podatak o 538 transportiranih bolesnika sa STEMI na području Sisačko-moslavačke županije od listopada 2005. do srpnja 2012. godine. Tijekom transporta do 70 kilometara udaljenog Zagreba umrlo je 5 bolesnika (<1%). Rizik mogućih komplikacija za vrijeme transporta bolesnika sa slikom kardiogenog šoka, srčanog popuštanja, hemodinamski ili aritmološki nestabilnih bolesnika je sigurno puno veći. Već je rečeno da kod ovih bolesnika pPCI ima prednost i treba ju favorizirati u odnosu na fibrinolitičku terapiju. Dilema koju mogu imati liječnici na terenu je da li bolesnika transportirati odmah ili ga prvo klinički stabilizirati. Podaci iz studije SHOCK[25] su ključni za preporuku američkih smjernica[17] da bolesnici s kardiogenim šokom trebaju neodložan transfer radi revaskularizacije, jer su bolesnici kojima je prvo pokušana medikamentozna stabilizacija stanja imali veći mortalitet. Ukupno 53% bolesnika uključenih u ovo ispitivanje bilo je transportirano prije učinjene revaskularizacije, a 49,3% revaskulariziranih bolesnika je prethodno dobilo fibrinolitičku terapiju.

Tranport bolesnika liječenih fibrinolitičkom terapijom u centar s mogućnosti perkutane koronarne intervencije učinjen od dobro educirane i opremljene ekipe ne povećava rizik za bolesnika i može se smatrati sigurnim.

Stav autora ovog članka je da se transport bolesnika treba organizirati odmah nakon injiciranja fibrinolitičke terapije. Fibrinolitik izbora je tenekteplaza kao fibrin specifični agens koji se daje jednokratno, što ga čini i najpoželjnijim fibrinolitikom za prehospitalnu primjenu. Za ostale lijekove koji se daju u kontinuiranoj infuziji također je moguće započinjanje transporta još za vrijeme davanja fibrinolitika, svakako uz davanje antitrombocitne i antikoagulacijske terapije.

Protokol zbrinjavanja bolesnika s akutnim infarktom miokarda s elevacijom ST-segmenta u zapadnoj Slavoniji

U ovom časopisu već su objavljena dva algoritma za transport bolesnika sa STEMI iz bolnica koje nemaju mogućnost liječenja pPCI i to za područje koje pokriva Klinički bolnički centar Zagreb[26] te algoritam Zavoda za kardiovaskularne bolesti Kliničkog bolničkog centra "Sestre milosrdnice" Zagreb[27]. Oba algoritma su praktički identična i kod odlučivanja o vrsti reperfuzijske terapije — fibrinolitička terapija se preporuča kod bolesnika koji se prezentiraju unutar 3 sata od početka bolova, a očekivano vrijeme do otvaranja žile mehaničkim putem je dulje od 90 minuta. Bolesnici s uspješnom fibrinolizom se trebaju uputiti na invazivnu obradu sutradan, dok bolesnici kod kojih nema znakova reperfuzije (perzistiranje elevacije, perzistiranje bolova, razvoj komplikacija) imaju indikaciju za rescue PCI i neodložan transport. Bolesnici kod kojih bol traje dulje od 3 sata, a manje od 12 sati u trenutku prezentacije su kandidati za pPCI i što brži transport u tercijarni centar.

is safe. This conclusion was also reached by *Gachoud et al*[1] that did not have any major complications during the transportation of 42 patients for pPCI. One of 300 patients with chest pains who were transported by private transport suffered cardiac arrest[22] during the transportation. *Straumann et al*[3] state that in a group of 68 high risk STEMI patients, among whom 17 of them had cardiogenic shock, 15 of them were resuscitated before the transportation and 8 of them were intubated during the transportation and none of them died during transportation which lasted for 55 (18 -115) minutes. *Balenović et al*[4] mention the detail that 538 patients with STEMI were transported in the region of the County of Sisak and Moslavina from October 2005 to July 2012. There were 5 patients (<1%) who died during the transportation up to 70 kilometers away from Zagreb (<1%). The risk of potential complications during the transport of patients with a diagnosis of cardiogenic shock, heart failure, or hemodynamically or arrhythmically unstable patients is certainly much higher. As already noted pPCI has advantage over and should be preferred to the fibrinolytic therapy in these patients. The dilemma that physicians can have on the field is whether a patient is to be transported immediately or clinically stabilized in the first place. The data from the SHOCK[25] study is key to the recommendation of the American guidelines[17] suggesting that patients with cardiogenic shock need a transfer for revascularization with no delay, because the patients in whom medicamentous stabilization of their condition was first attempted recorded higher mortality. A total of 53% of the patients included in this trial was transported before revascularization, and 49.3% of revasculated patients had previously received fibrinolytic therapy.

The transportation of patients treated with fibrinolytic therapy to the center capable of undertaking percutaneous coronary interventions performed by well-trained and equipped team do not increase the risk for patients and can be considered safe.

The attitude of the author of this article is that the transport of patients should be organized immediately after the injection of fibrinolytic therapy. Fibrinolytic drug of choice is tenecteplase as fibrin-specific agent that is administered only once, which makes it the most desirable fibrinolyc drug for prehospital usage. Regarding other drugs that are administered in a continuous infusion, the transportation may also start during the administration of fibrinolytic drug, certainly accompanied by administering antiplatelet and anticoagulant therapy.

Protocol of management of patients with STEMI in Western Slavonija

Two algorithms for transportation of STEMI patients from hospitals not having the pPCI treatment option, namely for the area covered by the University Hospital Centre Zagreb, Zagreb[26] and algorithm and the University Hospital Centre Sestre milosrdnice, Zagreb[27] have already been published in this journal. Both algorithms are practically identical and in deciding on the type of reperfusion therapy — fibrinolytic therapy is recommended in patients who were presented within 3 hours from the onset of pains, and the expected time until the opening the vessel mechanically is longer than 90 minutes. Patients with successful fibrinolysis should be directed to invasive treatment the next day, while the patients with no signs of reperfusion (elevation persistence, persistence of pains, development of complications) have indications for rescue PCI and transportation with no delay. Patients with pains lasting longer than 3 hours and less than

	Diagnosis of acute myocardial infarction with ST-segment elevation				
Time (hours): onset of pain-ECG	<3				>3-12 to undartake pPCI
Age (years)	<65		>65		
Infarct location	anterior	nonanterior	anterior	nonanterior	
Maximal PCI related delay* (minutes)	45	90	120	180	
Reperfusion strategy					pPCI

*PCI related delay = [expected duration of transport + 30 minutes for expected time for primary PCI] – expected time for starting fibrinolitic therapy.
pPCI = primary percutaneous coronary intervention.

Table 2. *Algorithm for reperfusion strategy for patients with acute myocardial infarction with ST-segment elevation in Western Slavonia.*

Predloženi algoritam pristupa bolesniku sa STEMI u zapadnoj Slavoniji (**Tablica 2**) još je u izradi i podložan je promjenama nakon što će biti prodiskutiran od svih članova multidisciplinarnog tima koji je uključen u zbrinjavanje bolesnika sa STEMI na području zapadne Slavonije. Ovaj tim čini ne samo bolnica s mogućnosti liječenja pPCI u Slavonskom Brodu, nego i kolege iz županijskih bolnica u Požegi i Novoj Gradiški te ekipe hitne medicinske pomoći iz čitave zapadne Slavonije. Cilj je napraviti jedinstven protokol za cijelo područje koji će omogućiti pružanje adekvatne reperfuzijske terapije što većem broju bolesnika sa STEMI, koji će davati jasna uputstva o zbrinjavanju, ali i destinacijski protokol svakom liječniku bez obzira na mjesto ulaska bolesnika sa STEMI u zdravstveni sustav. Postulati su da želimo razviti mrežu u kojem će na terenu ključnu ulogu u trijaži i transportu bolesnika imati služba hitne medicinske pomoći s jasnim destinacijskim protokolom, aktivacija tima za pPCI jednim pozivom s terena i direktni prijem bolesnika izravno u kateterizacijski laboratorij. U slučaju prezentacije bolesnika u bolnici bez mogućnosti liječenja pPCI ili kod liječnika hitne medicinske pomoći, ordinirajući liječnik donosi odluku o vrsti reperfuzijske terapije. Za liječnika hitne medicinske pomoći time je definiran i destinacijski protokol. Izborom pPCI kao reperfuzijske strategije preskače se najbliža bolnica ako nema mogućnost pPCI i bolesnik se transportira direktno u kateterizacijski laboratorij. O vrsti reperfuzijske strategije liječnik donosi odluku na osnovu trajanja ishemije, kliničkih karakteristika bolesnika (dob i lokalizacija infarkta) te očekivanog kašnjenja reperfuzije u slučaju izbora pPCI kao reperfuzijske terapije (vrijeme transporta i vrijeme potrebno za izvođenje pPCI umanjeno za vrijeme potrebno za započinjanje fibrinolize). Metoda pPCI je terapija izbora za svakog bolesnika ukoliko se može izvesti unutar zadanog vremena očekivanog kašnjenja pPCI. Ako je pPCI neizvodiva u zadanom vremenskom okviru za konkretnog bolesnika, primjenjuje se farmakoinvazivna strategija. Za hemodinamski ili aritmološki nestabilne bolesnike ili bolesnike u kardiogenom šoku favorizira se pPCI neovisno o vremenu trajanja ishemije. Za bolesnike kod kojih je farmakoinvazivna strategija metoda izbora, fibrinolitička terapija se započinje što ranije, najkasnije unutar 30 minuta. Favorizira se transport bolesnika odmah, neovisno o uspjehu fibrinolize, favorizira se

12 hours at the time of presentation are the candidates for pPCI and as fast transport to a tertiary center as possible.

The proposed algorithm of the approach to the patient with STEMI in Western Slavonia (**Table 2**) is still being developed and is subject to changes after being discussed by all the members of the multidisciplinary team involved in the management of patients with STEMI in the region of Western Slavonia. This team is composed not only of the hospital capable of performing pPCI in Slavonski Brod, but also colleagues from the county hospitals in Požega and Nova Gradiška and emergency medical service from the whole of Western Slavonia. The aim is to create a unique protocol for the entire region which will enable the provision of adequate reperfusion therapy to as many patients with STEMI as possible, which will give clear instructions about management, but also the destination protocol to every physician regardless of the point of entry of patients with STEMI in the health care system. The postulates are that we want to develop a network where a emergency medical service with a clear destination protocol will have a crucial role in triage and transportation of patients on the field, activation of the pPCI team by one call from the field and direct admission of patients directly to the catheterization lab. In the case of presentation of patients in the hospital not capable of performig pPCI or with EMC physician, the attending physician will decide on the type of reperfusion therapy. Destination protocol is thus defined for medical emergency center. By selecting pPCI as the reperfusion strategy, the nearest hospital is skipped if it is not capable of undertaking pPCI and the patient is transported directly to the catheterization lab. The type of reperfusion strategy is decided upon by a physician based on the length of ischemia, clinical characteristics of a patient (age and localization of myocardial infarction) and the expected delay of reperfusion in case of selection of pPCI as a reperfusion therapy (transportation time and the time required to perform pPCI less the time required for initiation of fibrinolysis). pPCI method is the therapy of choice for every patient if it can be performed within a set, that is, expected pPCI time delay. If pPCI is not feasible in a given time frame for a particular patient, pharmacoinvasive strategy is applied. Regardless of the length of ischemia, pPCI is a preferable treatment method for hemodynamically or ar-

transport i za vrijeme davanja fibrinolitičke terapije, a odluka o vremenu invazivne obrade nakon fibrinolize (rescue PCI ili rana invazivna strategija) je u domeni invazivnog kardiologa. Za bolesnike prezentirane u bolnici s mogućnosti pPCI, protokol uključuje snimanje i interpretaciju EKG-a unutar 10 minuta od prijma u objedinjeni hitni bolnički prijam i direktni ulazak u kateterizacijski laboratorij, bez prolaska kroz koronarnu jedinicu, s ciljnim vremenom do reperfuzije od 30 minuta.

Završetak prikaza slučaja

Muškarac u dobi 60 godina koji ima anteroseptalni infarkt s trajanjem ishemije od 40 minuta ima maksimalni "PCI-related delay" (vrijeme nakon kojeg se gubi prednost pPCI u odnosu na fibrinolitičku terapiju) od maksimalno 45 minuta. Očekivani "PCI-related delay" za ovog bolesnika u ovom trenutku iznosi 80 minuta (20 minuta do dolaska vozila hitne medicinske pomoći +45 minuta transporta do Slavonskog Broda +30 minuta do prolaska žicom kroz okluziju -15 minuta do početka ordiniranja alteplaze).

Liječnik u Požegi se odlučuje za farmakoinvazivnu strategiju. Bolesniku objašnjava način liječenja i dobiva pisani pristanak za invazivnu dijagnostiku i eventualnu PCI. Liječnik odmah organizira prijevoz bolesnika Opću bolnicu Slavonski Brod i pozivom na broj pripravnog interventnog kardiologa najavljuje dolazak bolesnika za oko 65 minuta. Bolesnik dobiva 300 mg acetilsalicilatne kiseline, 600 mg klopidogrela, 30 mg enoksaparina i.v., 15 mg alteplaze u obliku intravenskog bolusa i započinje se infuzija alteplaze tijekom 30 minuta. U međuvremenu dolazi vozilo hitne medicinske pomoći, bolesnik se u pratnji kompletnog medicinskog tima uz trajni EKG monitoring transportira do Slavonskog Broda. Tijekom transporta započinje se druga infuzija od 35 mg alteplaze tijekom 60 minuta. Transport protiče bez komplikacija, bolesnik bude primljen u Koronarnu jedinicu dok mu još teče fibrinolitička terapija. Bolesnik je kardijalno kompenziran, normotenzivan i ritmološki stabilan. Bol u prsima je vrlo blaga, sada intenziteta 2/10, 90 minuta nakon isteka fibrinolitičke terapije u V3 odvodu gdje je bila registrirana maksimalna elevacija ST-segmenta od 4mm sada je elevacija 1mm. Dežurni liječnik u Koronarnoj jedinici zaključuje da je reperfuzija uspješna, ali poziva ekipu za PCI koja se organizira 3 sata nakon isteka fibrinolitičke terapije. Nađe se 95% trombotska stenoza srednjeg segmenta prednje silazne koronarne arterije koja se bez komplikacija riješi primarnim stentingom.

Zaključak

Europske i američke smjernice za liječenje STEMI preporučuju organizaciju učinkovitog dobro organiziranog sustava skrbi koji se temelji na prehospitalnoj trijaži i brzom prijevozu u referalni centar sa mogućnošću liječenja pPCI. Cilj je dijagnosticirati STEMI što ranije i maksimalno skratiti vremena kašnjenja u pružanju reperfuzijske terapije što većem broju bolesnika. Metoda pPCI je nesumnjivo strategija izbora u liječenju STEMI, ali ako je izvediva u kratkom vremenskom roku od 90-120 minuta, za neke bolesnike i unutar 60 minuta od prezentacije bolesnika. U našoj svakodnevnoj praksi pokušaj da se bolesniku sa STEMI organizira pPCI povezan je s neprihvatljivo dugim kašnjenjima čime se gubi prednost pPCI u odnosu na fibrinolitičku terapiju. Izbor reperfuzijske strategije treba individualno prilagoditi svakom bolesniku i lokalnim uvjetima te mogućnostima rada. Im-

rhythmically unstable patients. For patients in whom pharmacoinvasive strategy is the method of choice, fibrinolytic therapy should be inititated as early as possible, within 30 minutes at the latest. The immediate transportation of patients is preferred, regardless of the success of fibrinolysis, the transportation during administration of fibrinolytic therapy is also preferred, and the decision about the time of invasive treatment after fibrinolysis (rescue PCI or early invasive strategy) is to be made by the invasive cardiologist. For patients present at the hospital capable of pPCI, the protocol includes recording and interpretation of ECG within 10 minutes from the admission to the integrated emergency hospital admission department and direct entry into the catheterization lab, without passing through the coronary unit with a 30 minutes' target time to reperfusion.

Completion of case study

A man aged 60 who has anteroseptal myocardial ischemia lasting for 40 minutes has a maximum PCI-related delay (time after which pPCI loses its advantage over fibrinolytic therapy) of a maximum of 45 minutes.

The expected PCI-related delay for this patient at this moment is 80 minutes (20 minutes till the arrival of ambulance +45 minutes of transportation to Slavonski Brod +30 minutes to the passage of the guide wire through the occlusion -15 minutes until the start of administration of alteplase).

A physician in Požega chooses a pharmacoinvasive strategy. The patient is explained the method of treatment and obtains a written consent to the invasive diagnostics and potentially PCI. The physician immediately organizes the transportation of a patient to the General Hospital Slavonski Brod and calling the number of attending interventional cardiologist he announces the arrival of the patient in about 65 minutes. The patient receives 300 mg acetylsalicylic acid, 600 mg of clopidogrel, 30 mg enoxaparin i.v., 15 mg of alteplase in the form of an intravenous bolus and the infusion of alteplase starts during the time of 30 minutes. In the meantime, the ambulance vehicle arrives, the patient accompanied by the complete medical team with continuous ECG monitoring is transported to Slavonski Brod. During the transportation, the second infusion of 35 mg alteplase starts during the time of 60 minutes. The transportation is carried out without complications, the patient is admitted to the Coronary Care Unit at the same time when the fibrinolytic therapy is in progress. There are no signs of heart failure, the patient is normotensive and rhythmologically stable. Chest pain is very mild, now with the intensity of 2/10, 90 minutes after the end of fibrinolytic therapy in the V3 lead where the maximum ST-segment elevation of 4 mm was registered, now the elevation is 1 mm. The attending physician in the Coronary Care Unit concludes that the reperfusion is successful, but calls the PCI team that is organized three hours after the end of fibrinolytic therapy. 95% of thrombotic stenosis of the mid anterior descending coronary artery is found, which is resolved without complications by primary stenting.

Conclusion

European and American guidelines for the treatment of STEMI recommend organizing an efficient well-organized system of management that is based on the prehospital triage and quick transportation to a referral center capable of treating pPCI. The aim is to diagnose STEMI as soon as possible and to shorten the delay time in providing reperfu-

plementiranje farmakoinvazivne strategije u regionalne protokole zbrinjavanja bolesnika sa STEMI bi povećalo broj bolesnika kojima je pružena pravilna i pravodobna primjena reperfuzijske terapije.

sion therapy to as many patients as possible. The pPCI method is undoubtedly a strategy of choice in the treatment of STEMI, but if it is feasible in the short time period of 90-120 minutes, for some patients even within 60 minutes from the moment of patient's presentation. In our daily practice an attempt to organize pPCI for a patient with STEMI is associated with unacceptably long delays which is why pPCI loses its preferenance to the fibrinolytic therapy. The choice of reperfusion strategy should be individually tailored to each patient and to local conditions and possibilities. Implementing the pharmacoinvasive strategies in regional protocols for the management of patients with STEMI would increase the number of patients who are given proper and timely reperfusion therapy.

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