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Primjena kisika u akutnom infarktu miokarda — nužno ili nepotrebno?

Application of oxygen in acute myocardial infarction — necessary or unnecessary?

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SAŽETAK: *Unazad nekoliko mjeseci u medicinskoj literaturi se ponovno intenzivno propituje korisnost uporabe liječenja kisikom u akutnom infarktu miokarda (AIM). Rezultati nekih novijih istraživanja ukazuju kako bi takvo liječenje moglo biti čak i štetno. Trenutno važeće Smjernice daju preporuke za primjenu liječenja kisikom u hipoksičnih bolesnika s AIM, pa je preporuka da se dalje toga pridržava.*

KLJUČNE RIJEČI: *kisik, akutni koronarni sindrom.*

SUMMARY: *During the last few months, the medical literature again started questioning the benefits of treatment with oxygen in acute myocardial infarction (AMI). The results of the most recent investigations show that such treatment may even be harmful. The currently applicable Guidelines provide recommendations for the treatment with oxygen in hypoxic patients with AMI, so they recommend further compliance therewith.*

KEYWORDS: *oxygen, acute coronary syndrome.*

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Unazad nekoliko mjeseci svjedoci smo sve intenzivnijeg propitivanja još jednog uvriježenog mišljenja u kardiologiji — korisnosti uporabe kisika u akutnom infarktu miokarda (AIM). Ono što je već niz godina općepoznato i općeprihvaćeno jest da se u AIM bolesniku treba što prije započeti liječenje kisikom, ponajprije zbog ideje da se ishemičnom miokardu što prije "pomogne" i poveća opskrba kisikom. Ovo je vidljivo iz radova koji opisuju svakodnevan praktični rad s bolesnicima s akutnim koronarnim sindromom (ACS) u Hrvatskoj[1-3], a tome se poučavaju i studenti medicine. No, iz današnje prespektive medicine temeljene na dokazima, praktički je nezamislivo da jedan lijek može biti toliko široko primjenjivan, a bez dovoljno čvrstih dokaza o korisnosti primjene.

Niz istraživanja, od kojih je većina učinjena u drugoj polovici 20. stoljeća, opsežno su proučavala kardiovaskularne učinke primjene povećane koncentracije kisika (hiperoksije). Uočeno je kako hiperoksija smanjuje protok krvi kroz koronarne arterije[4] uzrokujući vazokonstrikciju[5,6], smanjuje srčanu frekvenciju, minutni volumen[7,8] i potrošnju kisika od strane miokarda[9], ali i ukupnju tjelesnu potrošnju kisika[10] dok istovremeno povisuje arterijski tlak[11], sistemski vaskularni otpor i augmentacijski indeks (mjeru krutosti velikih arterija).

Danas se smatra da su dvije studije bile ključne za uvrštavanje kisika u smjernice za liječenje raznih oblika ACS[12,13]. Osnovno razmišljanje za kojim su se vodile te studije bila je korisnost primjene kisika s ciljem povećanja saturacije arterijske krvi što smanjuje akutnu ishemijsku oz-

During the last few months, we have witnessed more frequent questioning of another well established opinion in cardiology — the benefits of using oxygen in acute myocardial infarction (AMI). The fact that has been generally known and accepted for many years is that the AMI patient needs treatment with oxygen as soon as possible, first as a result of an idea that the ischemic myocardium needs to be helped as soon as possible with an increased supply of oxygen. This is visible from the articles that describe the daily practical work with patients suffering from acute coronary syndrome (ACS) in Croatia[1-3] and this is also what medical students are taught. However, from the today's evidence-based medicine it is almost unconceivable to imagine that one medicine may be so widely used without sufficient evidence of benefits from it.

A series of researches, whereas many of them were conducted in the second half of the 20th century, extensively investigated cardiovascular effects of the application of increased concentrations of oxygen (hyperoxia). It has been observed that hyperoxia reduces blood flow through coronary arteries[4] causing vasoconstriction[5,6], it reduces heart rate, minute volume[7,8] and consumption of oxygen by the myocardium[9], and also total body consumption of oxygen[10] while at the same time it increases blood pressure[11], systemic vascular resistance and augmentation index (measure of stiffness of large arteries).

Today, two studies are considered to be crucial for including oxygen in the guidelines for the treatment of different types of ACS[12,13]. The basic consideration used as guidelines for these studies was the benefit of using oxygen aimed at an increase in saturation of arterial blood with

ljedu i veličinu infarciranog područja miokarda. Primijećeno je da je kod nekih bolesnika s nekompliciranim AIM zabilježena arterijska hipoksemija zbog nakupljanja tekućine u plućima i nesrazmjera ventilacije i perfuzije. Međutim, studija provedena 1976. god. nije utvrdila dobrobit od primjene kisika u smislu smanjenja učestalosti aritmija ili mortaliteta, a čak se pokazalo i da je primjena kisika rezultirala povišenim razinama tada korištenog biljega oštećenja miokarda (aspartat aminotransferaza) sugerirajući povećanje infarcirane zone miokarda, a smrtnost je bila viša u skupini bolesnika koja je primala kisik (11,3% vs. 3,9%), no razlika nije bila statistički značajna[14]. U nedavno objavljenom radu ispitivani su učinci kisika na veličinu infarciranog miokarda te je zaključeno kako dokazi o učinkovitosti i sigurnosti liječenja kisikom sugeriraju kako rutinska primjena visokih doza kisika u nekompliciranom infarktu može uzrokovati povećanje zone infarkta, a moguće povećava i smrtnost[15].

Trenutno važeće Smjernice za liječenje ACS bez elevacije ST-segmenta Europskoga kardiološkog društva (ESC) kažu kako kisik treba primijeniti u dozi od 4-8 L/min samo ako je bolesnik hipoksičan (saturacija kisikom <90%)[16], dok ESC smjernice za liječenje AIM s elevacijom ST-segmenta iz 2008. god. za primjenu kisika u dozi od 2-4 L/min daju preporuku razreda I, razine dokaza C i to u slučaju zaduhe, znakova zatajivanja srca (stupanj ljestvice prema Killipu III i IV)[17]. Američke smjernice iz 2004. god. daju preporuku za primjenu kisika razreda I u slučaju hipoksije (saturacija kisikom <90%), ali i preporuku razine IIa za sve bolesnike s nestabilnom anginom pektoris, AIM bez elevacije ST-segmenta i nekompliciranim AIM s elevacijom ST-segmenta unutar prvih šest sati od kontakta s liječnikom[18]. U naknadnim dodatnim preporukama američkih smjernica iz 2007. i 2009. g. nisu davane dodatne preporuke ili mijenjane postojeće vezane uz primjenu kisika[19,20].

Prije nekoliko mjeseci objavljen je pregledni rad na tu temu od strane *The Cochrane Collaboration*[21]. Autori su rad napisali ponukani preglednim člancima koji sugeriraju moguću štetnost primjene kisika kod bolesnika s AIM i činjenicom da dosadašnji članci uglavnom zaključuju kako nema dovoljno dokaza kako bi se znalo je li primjena kisika smanjuje, povećava ili uopće nema učinka na ishemiju miokarda ili veličinu infarkta. Cilj autora bio je pregledati dokaze dostupne iz randomiziranih kontroliranih kliničkih ispitivanja kako bi utvrdili je li rutinska primjena kisika u AIM poboljšava ishode liječenja bolesnika, posebice bolova i smrti. Prema strogim kriterijima pretrage pronašli su svega tri istraživanja sa sveukupno 387 bolesnika, a zabilježeno je 14 smrtnih ishoda, s time da je u odnosu na one kod kojih je primijenjen kisik smrtni ishod bio tri puta češći. Iako je relativni rizik prema podacima iz ovih ispitivanja bio 2.88—3.03, zbog malog broja sudionika i ishoda, autori ne mogu isključiti da je ovaj rezultat ipak samo rezultat slučajnosti. Jačina bolova mjerila se putem uporabe analgetika te je relativni rizik bio 0.97. Ono što je, nažalost, problematično i što svakako treba uzeti u obzir prilikom interpretacije ovih podataka jest činjenica da, iako su primijenjeni strogi kriteriji za odabir prikladnih znanstveno valjanih studija, znanstvena metodologija korištena u ove tri studije bila je prilično slaba, s time da je jedna studija učinjena 1976.[14], druga 1997.[22], a treća 2005. god.[23]. Zaključak ovog pregleda je da nema dovoljno jakih

oxygen which reduces acute ischemic injury and the size of infarcted region of myocardium. It has been noticed that arterial hypoxemia was recorded in some patients with non-complicated AMI due to accumulation of fluid in the lungs and disproportion of ventilation and perfusion. However, the study conducted in 1976 did not show any benefit from the application of oxygen regarding reduction of frequency of arrhythmias or mortality, and it was shown that the application of oxygen resulted in higher levels of mark of myocardial damage used at that time (aspartate aminotransferase) suggesting an increase in infarcted zone of myocardium, while mortality was the highest in the group of patients that received oxygen (11.3% vs. 3.9%), but the difference was not statistically significant[14]. The recently publicized paper investigated the effects of oxygen on the size of infarcted myocardium and it was concluded that the evidence of efficiency and safety of treatment with oxygen suggests that routine application of high doses of oxygen in non-complicated infarction may cause an increase in the infarction zone, and possibly an increase in mortality[15].

The currently applicable Guidelines for the treatment of ACS without ST-segment elevation of the European Society of Cardiology (ESC) suggest application of oxygen in dose of 4-8 L/min only if a patient is hypoxic (oxygen saturation <90%)[16], while the ESC guidelines for the treatment of AMI with ST-segment elevation from 2008 for the application of oxygen in dose of 2-4 L/min recommend the class I, the level of evidence C in the event of dyspnoea, signs of heart failure (Killip III and IV class)[17]. The American guidelines from 2004 recommend application of oxygen of the class I in the event of hypoxia (oxygen saturation <90%), but they also suggest the level IIa for all patients with instable angina pectoris, AMI without ST-segment elevation of and non-complicated AMI with elevation of ST-segment within the first six hours from the contact with a doctor[18]. Subsequent additional recommendations of the American guidelines from 2007 and 2009 did not provide any additional recommendations or the existing recommendations relating to application of oxygen were not changed in these subsequent recommendations[19,20].

Several months ago, a review on this topic was publicized by The Cochrane Collaboration[21]. The authors wrote the article because they were encouraged by the reviews that suggest potential harm of application of oxygen with patients with AMI and the fact that the recent articles mainly provide a conclusion that there is insufficient evidence to prove whether the application of oxygen reduces, increases or generally has no effect on the ischemia of myocardium or the size of infarction. The authors' aim was to test the evidence available from randomized controlled clinical tests as to determine whether the routine application of the oxygen in AMI improves the outcomes of patients' treatment, especially pains and death. According to strict search criteria they found only three studies with a total number of 387 patients, and 14 mortality outcomes were recorded, whereas those who received oxygen showed the mortality outcome 3 times more frequently. Although a relative risk according to the data from these studies was 2.88-3.03, due to a small number of participants and outcomes, the authors could not exclude the fact that this result is only result of coincidence. Intensity of pains was measured by use of analgesics and the relative risk was 0.97. The thing, that is actually problematic, and that should definitely be considered during the interpretation of

dokaza koji bi u ovom trenutku poduprli rutinsku uporabu kisika kod bolesnika s AIM. Također se iz navedenoga iščitava snažna potreba da se što prije provede randomizirano kontrolirano kliničko ispitivanje s obzirom na prisutan nesrazmjer između trenutno dostupnih dokaza proizašlih iz postojećih kliničkih ispitivanja i preporuka za primjenu kisika koje se nalaze u trenutno važećim smjernicama za liječenje AIM. Iz tog razloga autori ovog pregleda su započeli pripreme za provođenje takvog kliničkog ispitivanja, čiji će rezultati svakako pomoći u razrješavanju ove dvojbe, a sve sa ciljem kako bi se bolesnike što bolje liječilo.

Međutim, kako ne bi bilo zabune, zaključak članaka[24,25] na ovu temu unazad nekoliko mjeseci jest kako se primjena u AIM ipak smatra razumnom, ponajprije zbog spoznaja iz fiziologije i manjka dokaza o štetnosti, no svakako u okviru preporuka trenutno važećih ESC smjernica. Na ova zbivanja ESC je reagiralo i izdalo priopćenje[26] u kojem navodi kako pozdravlja sve veći interes za ovu temu te kako će svakako dio novih smjernica za liječenje AIM s elevacijom ST-segmenta biti posvećen i ovoj temi. Naglašeno je kako trenutne Smjernice preporučuju primjenu kisika samo kod bolesnika koji su hipoksični, no kako nema jasnih preporuka treba li takvo liječenje primijeniti i kod bolesnika koji nisu hipoksični te da se do novog izdanja treba svakako držati postojećih preporuka.

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such data is the fact that, although strict criteria for the selection of adequate scientifically valid studies were applied, the scientific methodology used in these three studies was rather bad. There was one study conducted in 1976[14], while another was conducted in 1997[22], and the third was conducted in 2005[23]. The conclusion of this review is that there is insufficient evidence that would at the moment support routine use of oxygen with patients with AMI. The above mentioned implies that it is necessary to conduct randomized controlled clinical studies as soon as possible considering the present disproportion between the currently available evidence arising from the existing clinical sstudies and recommendations for the application of oxygen that are to be found in the currently applicable guidelines for the treatment of AMI. For that reason, the authors of this review started preparations for conducting a clinical study the result of which will definitely help in resolving this doubt, all aimed at providing better treatment for patients.

However, as to avoid any confusion, the conclusion reached from the articles[24,25] in the lasts several months is that the application of oxygen is considered reasonable, mainly, because of knowledge of physiology and lack of information on harmfulness, but certainly within recommendations of currently applicable ESC guidelines. The ESC has reacted to this and made a statement[26] welcoming ever greater interest for this topic and stating that one part of the new guidelines for the treatment of AMI with ST-segment elevation will certainly be dedicated to this topic as well. It has been emphasized that the current Guidelines recommend the application of oxygen only in patients who are hypoxic, but since there are no clear recommendations if such treatment should be applied even with patients who are not hypoxic, the existing recommendations should be definitely followed prior to the new issue thereof.

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