

## Poremećaj funkcije miokarda u teškoj sepsi i septičkom šoku

### Myocardial Function Depression in Severe Sepsis and Septic Shock

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**SAŽETAK:** Depresija funkcije miokarda uobičajeni je i najvažniji dio reakcije srčano-žilnoga sustava u neprimjerenom odgovoru imunskog sustava na infekciju, zvanom sepsa. Uz disfunkciju drugih organa još se češće poavljuje u teškoj sepsi i septičkom šoku s visokom stopom smrtnosti i do 70%. Identificirano je više čimbenika (genskih, molekularnih, staničnih, metaboličkih, jatrogenih) koji sudjeluju u nastanku, patogenezi i ishodu tog poremećaja, ali specifičan uzrok ostaje nerazjašnjen. Potrebna su dodatna integrativna istraživanja koja bi raščlanila i omogućila razumijevanje hijerarhije različitih mehanizama koji se javljaju u kompliciranoj sepsi općenito, te u srcu u tom kontekstu. Najprominentniji oblik sa smanjenjem kontraktilnosti, ejeckijske frakcije i dilatacijom lijeve klijetke često se naziva septička kardiomiopatija. Disfunkcija miokarda u sepsi je, cjelovito gledano, karakterizirana prolaznom globalnom (sistolikom i dijastolikom) disfunkcijom lijeve i desne strane srca koja se javlja u uvjetima komplicirane sepse, unatoč adekvatnoj nadoknadi tekućine i vazopresora te traje 7 do 10 dana ukoliko dođe do oporavka pacijenta. Najvažniji postupak za dijagnosticiranje disfunkcije miokarda jest ehokardiografija koja uz dijagnozu omogućuje praćenje i adekvatno liječenje pacijenta. Prestaje dodatna valorizacija i nekih biokemijskih nalaza poput troponina i B-tip natriuretskog peptida koji već imaju značajnu ulogu u ranoj dijagnostici disfunkcije miokarda. Ne postoji specifično liječenje disfunkcije miokarda u sepsi već je ono sastavni dio terapijskoga pristupa samoj sepsi s komplikacijama odnosno rana antibiotska terapija uz eventualno kirurško odstranjenje infektivnoga žarišta. Simptomatska terapija predstavlja ranu i brzu nadoknadu volumena tekućine uz primjenu vazopresorne i inotropne terapije. Ciljano liječenje disfunkcije miokarda i kardioprotekcije u kompliciranoj je sepsi predmet intenzivnih istraživanja.

**SUMMARY:** Myocardial function depression is the common and most important part of the cardiovascular system reaction in the immune system's unsuitable response to an infection, known as sepsis. Along with the dysfunction of other organs it is even more common in cases of severe sepsis and septic shock, and has a high mortality rate that can reach up to 70%. A number of factors that have been identified (genetic, molecular, cellular, metabolic, iatrogenic) contribute to the development, pathogenesis, and outcome of this disorder, but the specific cause remains unclear. Further integrative research is needed in order to analyze and clarify the hierarchy of various mechanisms that occur in complicated sepsis in the heart and in general. The most prominent form that includes reduced contractility, ejection fraction, and dilation of the left ventricle is often called septic cardiomyopathy. Myocardial dysfunction in sepsis is, on the whole, characterized by a temporary global (systolic and diastolic) dysfunction of the left and right sides of the heart, which occurs in complicated sepsis despite a resupply of adequate amounts of fluids and vasopressors and lasts from 7 to 10 days in case of the patient's recovery. The most important method for diagnosing myocardial dysfunction is echocardiography, which makes possible the monitoring and suitable treatment of the patient. There is a need for additional evaluation of some biochemical results, such as troponin and B-type natriuretic peptide, which already have a significant role in early diagnosis of myocardial dysfunction. There is no specific treatment for myocardial dysfunction in sepsis. Instead, it is integrated in therapeutical approach to sepsis with complications or, in other words, an antibiotic therapy with a possible surgical removal of the infected focus. Symptomatic therapy represents an early and rapid resupply of fluids with an application of vasopressors and an inotropic therapy. A treatment aimed at myocardial dysfunction and cardioprotection in complicated sepsis is the subject of intense research.

**KLJUČNE RIJEČI:** septička kardiomiopatija, teška sepsa, septički šok, disfunkcija miokarda, srčano zatajivanje.

**KEYWORDS:** septic cardiomyopathy, severe sepsis, septic shock, myocardial dysfunction, heart failure.

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## Uvod

Sepsa je sindrom<sup>1</sup> koji se po prvi puta definira kao sustavni upalni odgovor na infekciju 1992. godine<sup>2</sup>. Često se komplicira nedovoljnom perfuzijom tkiva, disfunkcijom organa i hipotenzijom, što predstavlja tešku sepsu, a kad je ta hipotenzija rezistentna na adekvatnu primjenu intravenske tekućine, to stanje nazivamo septičkim šokom<sup>3</sup>. Teška sepsa i septički šok su ozbiljna stanja s visokom smrtnošću. U istraživanju sepse, u koje je bila uključena 21 europska zemlja tijekom 15 dana 2002. godine, smrtnost pacijenata sa sepsom je iznosila 27%, a u onih sa septičkim šokom više od 50%<sup>4</sup>. To je sindrom 21. stoljeća čija učestalost raste i koji uzrokuje najviše smrti među bolničkim pacijentima, što je paradoksalna posljedica produljenja života opće populacije, ali i pacijenata koji bi bez suvremenog pristupa liječenju (mehanička ventilacija, imunosupresivna terapija, invazivni postupci) umrli, no upravo zbog toga su podložniji infekcijama.

## Sepsa i srce

Cjelokupni kardiovaskularni sustav sudjeluje u patofiziološkim procesima u teškoj sepsi i septičkom šoku<sup>5</sup>. Unatoč tome točna učestalost poremećaja srčane funkcije u tom kontekstu ostaje nepoznata zbog nedostatka većih epidemioloških studija, ali i konsenzusa o nomenklaturi, a i definiciji istoga<sup>6</sup>. Premda je već dugo poznat<sup>7,8</sup>, poremećaj funkcije miokarda ne označuje se jednoznačno već ima različite nazive: disfunkcija miokarda, depresija miokarda u sepsi, septička kardiomiopatija, kardiomiopatija inducirana sepsom, globalna hipokinezija ili akutna dilatacija lijeve klijetke (LK) izazvana sepsom<sup>6,9-12</sup>. Već u ranim istraživanjima konfuziju je izazvala podjela šoka u sepsi, zbog ograničenja tadašnje tehnologije, na dvije faze "toploga" (hiperdinamskoga) i "hladnoga" (hipodinamskoga) šoka koje su se temeljile na različitim kliničkim, ali i hemodinamskim karakteristikama<sup>13,14</sup>. Oba su stanja karakterizirana smanjenim sistemnim vaskularnim otporom, što je temeljna karakteristika hemodinamike u sepsi, no u „toplom“ je, za razliku od „hladnoga“, depresija miokarda prikrivena adekvatnom primjenom tekućine, što dovodi do održanja ili čak povećanja srčanoga minutnog volumena i kardijalnoga indeksa. Korištenjem radionuklidne cineangiografije kod pacijenata sa septičkim šokom, uz adekvatnu nadoknadu tekućine, naknadno je dokazano da i u tom stanju postoji značajna depresija funkcije miokarda uz smanjenje ejekcijske frakcije (EF) i udarnog volumena te povećanje teledijastoličkoga volumnog

## Introduction

Sepsis<sup>1</sup> is a syndrome identified for the first time in 1992<sup>2</sup> as a systemic inflammatory response to infection. It often leads to insufficient tissue perfusion, organ dysfunction, and hypotension, which represents severe sepsis, and in cases when hypotension is resistant to intravenous fluids this condition is called septic shock<sup>3</sup>. Severe sepsis and septic shock are serious conditions with a high mortality rate. In 2002, a study that included 21 European countries over a period of 15 days revealed that the mortality rate of patients with sepsis was 27%, while the mortality rate of patients in septic shock was 50%<sup>4</sup>. Being an increasingly common syndrome of the 21st century, sepsis causes the highest number of deaths among hospital patients, which is, paradoxically, a consequence of the increase in life expectancy among the general population, but also among patients who would die without contemporary health care (mechanical ventilation, immunosuppressive therapy, invasive procedures), but who are thus more likely to contract an infection.

## Sepsis and the heart

The entire cardiovascular system participates in pathophysiological processes in cases of severe sepsis and septic shock<sup>5</sup>. Despite this, the exact prevalence of the depression of cardiac function in this context remains unknown due to a lack of major epidemiological studies and a consensus on nomenclature and the definition<sup>6</sup>. Although it has long been recognized<sup>7,8</sup>, there is no single name for the depression of the myocardial function. Instead, it is known by several terms: myocardial dysfunction, myocardial depression in sepsis, septic cardiomyopathy, sepsis-induced cardiomyopathy, global hypokinesia, or acute dilatation of left ventricle caused by sepsis<sup>6,9-12</sup>. Due to limitations in technology, there was confusion in earlier research regarding the division of septic shock into the phases of "warm" (hyperdynamic) and "cold" (hypodynamic) shock, which was based on different clinical and hemodynamic characteristics<sup>13,14</sup>. Both conditions are characterized by a reduction in systemic vascular resistance, which is the basic characteristic of septic hemodynamics. However, unlike in the "cold" phase, in the "warm" phase the myocardial depression is masked by the application of adequate amounts of fluid, which leads to persistance or even an increase in the cardiac output and cardiac index. By using radionuclide cineangiography in patients with septic shock and by replacing adequate amounts of fluid it was subsequently proven that

indeksa (*end-diastolic volume index*)<sup>15,16</sup>. Upravo zahvaljujući tim pionirskim istraživanjima srčana se disfunkcija u sepsi često i danas promatra i identificira prvenstveno sa sistoličkom (dis)funkcijom LK odnosno kompromitiranjem EF iste, a koja je predstavljala jednostavnu mjeru kontraktilnosti LK. Taj se poremećaj označava često pojmom septičke kardiomiopatije<sup>17</sup>. Razlozi te simplifikacije nisu, čini se, posljedica samo povijesnih tehničkih aspekata i ograničenja<sup>15</sup> jer je ista paradigma i sada prilično prisutna unatoč dostupnosti i dosezima suvremene ultrazvučne tehnologije. Iako je smanjenje EF najeklatantniji oblik disfunkcije miokarda u sepsi, ni Europsko ni Američko kardiološko društvo nisu u svoje klasifikacije još uvijek uveli pojam septičke kardiomiopatije<sup>18,19</sup>, niti je postignut konsenzus koja bi to razina smanjenja EF bila.

Disfunkcija miokarda u kompliciranoj sepsi je ipak puno složenija, tim više što EF može biti i naizgled normalna u uvjetima jako sniženog arterijskog tonusa odnosno smanjenog tlačnog opterećenja (*afterload*) koji privremeno kompenzira smanjenje kontraktilnosti miokarda. Upravo zbog utjecaja i ovisnosti EF o volumnom (*preload*) i tlačnom opterećenju, nije dovoljno promatrati samo EF kao jedinu mjeru disfunkcije miokarda u sepsi što se nadilazi korištenjem tehnikama koje su neovisne o opterećenju. Novija ehokardiografska istraživanja su potvrdila oslabljenu i sistoličku i diastoličku funkciju LK septičkih pacijenata<sup>20,21</sup>. Suvremeni pristup shvaćanja poremećaja srčane funkcije u sepsi uzima u obzir poremećaj kontraktilnosti i relaksacije lijeve, ali i paralelno desne klijetke kao dijelove jednog spektra koji se mogu pojaviti izolirano, ali i u različitim kombinacijama<sup>17,22-24</sup>, a prolaznog su karaktera vremenski ograničenoga do 10 dana<sup>12</sup>. Učestalost tako definirana poremećaja funkcije miokarda u teškoj sepsi i septičkom šoku je oko 50%, pa i više, u istraživanju *Pulida i sur.* na 106 pacijenata je bila 64%<sup>11,20,22</sup>. U recentno objavljenom istraživanju *Orde i sur.* su usporedili konvencionalnu i noviju i osjetljiviju ultrazvučnu metodu tzv. *speckle tracking echocardiography* te na 60 pacijenata s teškom sepsom i septičkim šokom ustanovili značajnu razliku učestalosti poremećene funkcije miokarda u teškoj sepsi i septičkom šoku. Ovisno o metodi utvrđeno je da njih 33% odnosno 69% ima disfunkciju LK, a disfunkciju desne klijetke 32% odnosno 72% pacijenata<sup>25</sup>.

## Patogeneza depresije funkcije miokarda u sepsi

Poremećaj funkcije miokarda u sepsi predstavlja hemodinamski stres i posljedičnu dinamičku prilagodbu srčano-žilnoga sustava u sustavnom upalnom odgovoru organizma na infekciju<sup>22</sup>. Patofiziologija tog procesa je složena od tri paralelna neodvojiva zbivanja koji utječu međusobno jedni na druge: same infekcije, (sustavnog) odgovora, uključivo i srca, na infekciju te poduzetoga liječenja. Teška sepsa i septički šok predstavljaju složeni srčano-žilni, imunološki i metabolički događaj s genskim, molekularnim, funkcionalnim i strukturalnim promjenama i poremećajima više organskih sustava<sup>17,26-28</sup>.

Patofiziološki procesi i mehanizmi, kao i njihovi uzroci koji dovode do disfunkcije miokarda u sepsi, nisu u potpu-

this condition also leads to considerable myocardial depression, a reduction in ejection fraction (EF) and stroke volume, and an increase in end-diastolic volume index<sup>15,16</sup>. As a result of these pioneering studies, cardiac dysfunction in sepsis is still often observed and identified primarily by systolic (dys)function of the left ventricle or by compromising its EF, which represented a simple measurement of the contractility of the left ventricle. This disorder is often called septic cardiomyopathy<sup>17</sup>. It appears that the reasons for this simplification are not solely a result of historical technical limitations<sup>15</sup>, because the same paradigm is quite common today despite the availability of contemporary ultrasonic technology. Although EF reduction is the most obvious form of myocardial dysfunction in sepsis, neither the European nor the American Society of Cardiology have so far included the term septic cardiomyopathy<sup>18,19</sup> in their classifications, nor has there been a consensus on the amount of EF reduction.

Myocardial dysfunction in complicated sepsis is much more complex because the EF can appear to be normal in cases of extremely reduced arterial tonus and reduced afterload, which temporarily compensates for the reduced myocardial contractility. Due to the influence and dependency of EF on preload and afterload it is not enough to observe EF as the sole measurement of myocardial dysfunction in sepsis, which is avoided by using techniques independent of the load. More recent echocardiographic research has confirmed that both systolic and diastolic functions of the left ventricle are reduced in septic patients<sup>20,21</sup>. The contemporary approach to understanding cardiac disorder in sepsis takes into consideration the disorder in the contractility and relaxation of both the left and the right ventricle in parallel as parts of a spectrum that can appear in isolation, but in different combination as well<sup>17,22-24</sup>, and which are temporary, lasting up to 10 days<sup>12</sup>. The frequency rate of myocardial dysfunction defined as such is around 50% or more, while *Pulida et al.* showed on 106 patients the frequency rate of 64%<sup>11,20,22</sup>. In a recent study *Orde et al.* compared the conventional method with the newer, more sensitive echocardiographic one known as speckle tracking echocardiography. The study was carried out on 60 patients with severe sepsis and septic shock, and showed a significant difference in the frequency rate of myocardial dysfunction. It was found, depending on method, that 33% vs. 69% of patients had a dysfunction of the left ventricle, while 32% vs. 72% of them had a dysfunction of the right ventricle, respectively<sup>25</sup>.

## Pathogenesis of myocardial depression in sepsis

Myocardial dysfunction in sepsis represents hemodynamic stress and the resulting dynamic adaptation of the cardiovascular system in the systemic inflammatory response of the organism to the infection<sup>22</sup>. The pathophysiology of this process is composed of three parallel and inseparable processes that affect each other: the infection itself, (systemic) response to the infection that includes the heart, and medical treatment. Severe sepsis and septic shock represent a complex cardiovascular, immunological, and metabolic event with genetic, molecular, functional, and structural changes and dysfunction of a number of organ systems<sup>17,26-28</sup>.

nosti poznati, niti istraženi. Izravna zahvaćenost miokarda sa strukturnim patoanatomskim promjenama poput, mio-karditisa, apscesa, bakterijske kolonizacije i nekroze tkiva zasigurno mogu izazvati disfunkciju miokarda<sup>27,29</sup>. No takve, strukturne promjene ne objašnjavaju veći dio srčane disfunkcije u sepsi<sup>30</sup>. Povišena razina troponina, koja se često javlja u sepsi i istražuje kao prognostički čimbenik<sup>31,32</sup>, smatra se češće posljedicom povećane propusnosti membrane miokarda u sepsi nego nekroze<sup>33</sup>. Pretpostavka mehanizma nastanka poremećaja funkcije miokarda je pripisivanja ishemiji miokarda, što se ni na animalnim niti na ljudskim modelima nije pokazalo istinitom<sup>34,35</sup>. Već je početkom istraživanja uloge kardiovaskularnoga sustava u sepsi postavljena još jedna hipoteza: ona o postojanju cirkulirajućega čimbenika koji izaziva depresiju funkcije miokarda u teškoj sepsi<sup>8</sup>, što je tek godinama kasnije i dokazano<sup>36,37</sup>. Izraz je to koji se sve manje koristi, a nastoji se više ili manje točno zamijeniti identificiranim čimbenicima koji sami ili u kombinaciji mogu izazvati disfunkciju miokarda. Razmatranje, pa čak i ograničeno, pojedinog kandidata za cirkulirajući depresor srčane funkcije, nadilazi opseg ovog rada, pa ćemo samo spomenuti neke od najčešće istraživanih. Endotoksin nastaje kao posljedica lize gram-negativnih bakterija<sup>38,39</sup> te dovodi do otpuštanja drugih posrednika, uglavnom citokina TNF- $\alpha$ <sup>40</sup> i IL-1<sup>41</sup> te IL-6, ali i drugih poput komponenti komplementa C5a i C3 koji mogu izazvati disfunkciju miokarda. Jedan od najvažnijih receptora putem kojih djeluju je *toll-like* receptor-4 koji aktivira nuklearni faktor kappa B koji kontrolira ekspresiju gena za citokine<sup>42</sup>. U poremećaju disfunkcije miokarda u sepsi, uz navedene čimbenike i mehanizme, djeluju još mnogi drugi, bilo kao još jedan „osumnjčeni“ da je neposredni uzročnik ili posrednik. Patofiziološki mehanizmi koji sudjeluju u tom procesu nisu do kraja razjašnjeni, a u njima, uz spomenute, sudjeluju poremećaj autonomne regulacije (prekomjerna stimulacija katekolaminima), smanjenje vaskularnog tonusa, apsolutna ili relativna hipovolemija, apoptoza, metaboličke promjene (smanjenje iskorištenja glukoze, ketona i slobodnih masnih kiselina, poremećaj iskorištenja kisika). Još su složenije promjene i procesi gledani na staničnoj i molekularnoj razini koje zahvaćaju endotel s adhezijskim molekulama, postreceptorske signalne puteve, mitohondrije i sarkoplazmatski retikulum, natrijeve, kalcijeve i kalijeve kanale, sintetazu dušičnog oksida, endotelin-1, matriks metaloproteinaze, slobodne radikale kisika, kao i dodatne, a zainteresirane upućujemo na odlične pregledne radove<sup>10,17,43,44</sup>. Potrebna su dodatna integrativna istraživanja koja bi raščlanila i omogućila razumijevanje hijerarhije različitih mehanizama koji se javljaju u kompliciranoj sepsi općenito, te u srcu u tom kontekstu<sup>45</sup>.

## Klinički aspekt

Prolazno zatajivanje srčane funkcije je vrlo često kao sastavni dio teške sepse i septičkoga šoka s visokim mortalitetom koji iznosi i do 70%<sup>46</sup>. U navedenim kliničkim uvjetima mogu se očekivati različite, većinom prolazne, elektrokardiografske promjene poput smanjenja amplitude i produljenja QRS-a, (in) kompletni blok grane, promjene ST-segmenta, produljenja QTc intervala, koje nisu do kraja definirane, ali svraćaju pozornost na poremećaje depolarizacije i repolarizacije miokarda<sup>47-49</sup>.

Pathophysiological processes and mechanisms, as well as their causes, that lead to myocardial dysfunction in sepsis have not yet been understood or researched in their entirety. Myocardium affected directly by structural pathoanatomic changes such as myocarditis, abscesses, bacterial colonization, and tissue necrosis can certainly lead to myocardial dysfunction<sup>27,29</sup>. However, such structural changes do not explain the majority of cardiac dysfunction in sepsis<sup>30</sup>. An increase in the level of troponin, common in sepsis and studied as a factor in prognosis<sup>31,32</sup>, is often considered a result of an increased porosity of the myocardial membrane in sepsis, rather than a consequence of necrosis<sup>33</sup>. It was assumed that the mechanism behind the onset of myocardial disorder was a result of myocardial ischemia, which was proven false through testing carried out on animal and human models<sup>34,35</sup>. Early on in research of the role of the cardiovascular system in sepsis, another hypothesis was put forward: the existence of a circulating factor which causes the depression of the myocardial function in severe sepsis<sup>8</sup>, which was proven several years later<sup>36,37</sup>. This term is used less and less, and there has been an attempt to be replaced by identified factors which can, in isolation or in combinations, cause myocardial dysfunction. Even a limited consideration of each candidate for the myocardial depressant factor in sepsis is beyond the scope of this study, so we will only mention some of the most commonly researched ones. Endotoxin is created as a consequence of the decomposition of gram-negative bacteria<sup>38,39</sup> and leads to the release of other intermediaries, mostly cytokines TNF- $\alpha$ <sup>40</sup>, IL-1<sup>41</sup> and IL-6, and others such as the components of complements C5a and C3 which cause myocardial dysfunction. One of the most important receptors through which they function is the toll-like receptor-4, which activates nuclear factor kappa B that controls gene expression for cytokines<sup>42</sup>. Along with the listed factors and mechanisms, there are many others involved in myocardial dysfunction in sepsis, sometimes suspected of being a causative agent or an intermediary ones. Pathophysiological mechanisms involved in this process have yet to be fully explained. Along with the abovementioned effects, they also include the disorder of autonomic regulation (catecholamine overstimulation), reduced vascular tonus, absolute or relative hypovolemia, apoptosis, metabolic changes (reduced utilization of glucose, ketone and free fatty acids, disorder in the utilization of oxygen). Even more complex are the changes and processes on the cellular and molecular levels which target endothelium with adhesion molecules, postreceptor signal pathways, mitochondria and sarcoplasmic reticulum, sodium, calcium and potassium channels, nitrous oxide synthase, endothelin-1, matrix metalloproteinase, free oxygen radicals, etc. More information can be found in excellent existing reviews<sup>10,17,43,44</sup>. There is a need for additional integrative studies which would enable the better understanding of the hierarchy of different mechanisms that occur in complicated sepsis in general, and in the heart in that context<sup>45</sup>.

## Clinical aspects

Reversible heart failure often occurs as a part of severe sepsis and septic shock with a high mortality rate of up to 70%<sup>46</sup>. In these clinical conditions various and mostly electrocardiographic changes can occur, such as decreased QRS amplitude, widening of QRS complex, (in)complete branch block, changes in the ST-segment, QTc interval prolongation, none of which



Ehokardiografija je dijagnostički postupak izbora za procjenu bilo kojega hemodinamski kompromitiranoga pacijenta, što i jest pacijent s teškom sepsom i septičkim šokom po definiciji. Ona omogućuje praćenje adekvatne intenzivne terapije nadoknade tekućine koja smanjuje komplikacije bolesti, ali i smrtnost<sup>50</sup>, a ujedno i utvrđivanje odgovora na terapiju tekućinom (izbjegavanje prevelikog volumnog opterećenja) praćenjem promjena promjera donje šuplje vene ovisno o ciklusu disanja<sup>51</sup>. Za to se, naime, nisu pokazali dovoljno adekvatnim uobičajeni parametri praćenja: centralni venski tlak i tlak u plućnoj arteriji putem Swan-Ganzova katetera koji i dalje ostaju sastavni dio praćenja hemodinamski kompromitiranoga pacijenta. Ultrazvučno se mogu odrediti, uz globalno smanjenje kontraktibilnosti, i segmentalni poremećaji kontraktibilnosti, ali i diastolička disfunkcija obje klijetke<sup>12,22,52</sup>. Okolnosti otpuštanja troponina su već spomenute, no praćenje njegovih vrijednosti, kao i onih B-tip natriuretskoga peptida (BNP), kojega otpuštaju kardiomiociti u uvjetima naprežanja stijenke, ali i CRP-a, imaju vrijednu dijagnostičku i prognostičku vrijednost koja je još uvijek predmet istraživanja i valoriziranja<sup>31,53-55</sup>.

## Terapijski pristup

Ne postoji specifično liječenje disfunkcije miokarda u sepsi već je ono sastavni dio terapijskoga pristupa izravno sepsi s komplikacijama, a dobar temelj za to predstavljaju smjernice za pristup pacijentu s teškom sepsom i septičkim šokom<sup>3</sup>. Ovdje ćemo razmotriti načelni pristup terapiji sepsi i disfunkciji miokarda, a za detaljnije detalje upućujemo na pregledne članke na tu temu<sup>10,17,50</sup>.

Prvenstveni cilj je zaustaviti i izliječiti infekciju brzom (unutar jednoga sata od dijagnoze komplicirane sepse) primjenom empirijske intravenske antibiotske terapije i, ako je to moguće, odstraniti infektivno žarište kirurškim postupkom uz pokušaj identifikacije uzročnika. Osiguranje srednjeg arterijskog tlaka iznad 65 mmHg po spomenutim smjericama dovest će do uspostave zadovoljavajuće perfuzije tkiva, što će se postići brzo i dovoljnom količinom tekućine, inicijalno uglavnom kristaloida, uz albumin u slučaju potrebe velikih količina istih. Pri razvoju šoka potrebno je primijeniti vazopresornu terapiju. Preporučuje se korištenje noradrenalina kao vazopresora prvog izbora uz dodatnu primjenu adrenalina ili vazopresina bilo s ciljem povećanja srednjeg arterijskog tlaka ili smanjenja doze noradrenalina. Dopamin se preporučuje kao alternativa noradralinu samo u pažljivo odabranih pacijenata s niskim rizikom od tahiaritmija ili kod apsolutnih ili relativnih bradikardija. Povećanje tlakova punjenja i daljnji niski udarni volumen odnosno perzistencija znakova hipoperfuzije, unatoč adekvatnom intravaskularnom volumenu i srednjem arterijskom tlaku, govori u prilog da se razvija disfunkcija miokarda i da je indiciran pokušaj primjene inotropne terapije odnosno dobutamina. Središnji venski tlak je potrebno održavati između 8 i 12 mmHg, satnu diurezu iznad 0,5 mL/kg i saturaciju kisikom gornje šuplje vene iznad 65 do 70%. Dodatne terapijske mogućnosti su primjena selektivne oralne i digestivne dekontaminacije, hidrokortizona, transfuzije eritrocita kao i mehanička ventilacija, sedacija, analgezija, neuromuskularna blokada, profilaksa duboke venske trom-

have been sufficiently defined, but do indicate the presence of disorders of myocardial depolarization and repolarization<sup>47-49</sup>. Echocardiography represents a diagnostic method of assessing any hemodynamically compromised patient, such as a patient with severe sepsis and septic shock is. It enables a suitable aggressive fluid resuscitation implementation which reduces the chance for complications and death<sup>50</sup>. It also allows he to determination of the response determination to the fluid therapy (avoiding volume overload) by following the changes in the diameter of the inferior vena cava depending on the breathing cycle<sup>51</sup>. The commonly used parameters were found unsuitable in these circumstances: namely, the central vein pressure and the pressure in the lung artery through the Swan-Ganz catheter, which remain an important component of a hemodynamically compromised patient diagnostic and treatment procedures. Beside evaluation of a global reduction of contractility, ultrasound is used to determinate segmental contractility disorders and the diastolic dysfunction of both ventricles<sup>12,22,52</sup>. The circumstances in which troponin is released have already been mentioned, but following up its values, as well as the values of B-type natriuretic peptide (BNP) released by cardiomyocytes in cases of wall strain together with CRP, has a high diagnostic and prognostic importance which is still being researched and evaluated<sup>31,53-55</sup>.

## Therapeutic approach

There is no specific treatment for myocardial dysfunction in sepsis. Rather, it is an integrative part of a standard therapeutic approach to sepsis with complications, and a solid groundwork for this are the guidelines for treating a patient with severe sepsis and septic shock<sup>3</sup>. In this review we shall consider the essentials of a therapeutical approach to treating sepsis and myocardial dysfunction in sepsis, while more information can be found in the review articles on this topic<sup>10,17,50</sup>.

The main goal is to discontinue and cure the infection with a rapid application (executed within one hour of diagnosing complicated sepsis) of an empiric intravenous antibiotic therapy and, if possible, remove the infected focus through surgical treatment while attempting to identify the cause. By maintaining a medium arterial pressure above 65 mmHg according to the abovementioned guidelines, a satisfying tissue perfusion will be achieved by a rapid supply of a sufficient amount of fluid, initially mostly crystalloids, with albumin in case are required in large quantities. In case of shock, it is necessary to apply vasopressor therapy. Noradrenaline should be used as a vasopressor of first choice with an additional application of adrenaline or vasopressin, whether to increase the medium arterial pressure or decrease the dosage of noradrenaline. Dopamine is recommended as an alternative to noradrenaline only in carefully selected patients with a low risk of tachyarrhythmia or in absolute or relative bradycardia. An increase in filling pressures and further low stroke volume or signs of hypoperfusion, despite a sufficient intravascular volume and medium arterial pressure, attest to the fact that myocardial dysfunction is being developed and that an attempt to apply inotropic therapy, or dobutamine, is indicated. Central arterial pressure needs to be maintained at a value between 8 and 12 mmHg, hourly diuresis above 0.5 ml/kg and oxygen saturation of the superior vena cava above 65 to 70%. Additional therapeutic options include the application of selec-

boze, H2 blokatori, inhibitori protonске pumpe i nadomjesno bubrežno liječenje<sup>3</sup>.

Uz navedene terapijske mogućnosti postoje još neke usmjerene bilo na sepsu bilo izravno na poboljšanje srčane funkcije u sepsi koje se već koriste, a da nisu sadržane u smjericama ili su pak u eksperimentalnoj fazi. Levosimendan je vazodilatator koji ima i pozitivno inotropno djelovanje koji povećava osjetljivost kontraktilnih miofilamenata na kalcij i dovodi do poboljšanja parametara srčane funkcije u pacijenata sa septičkim šokom<sup>56</sup>. Još se istražuje zaštitno djelovanje blokatora beta receptora<sup>57</sup>, statina<sup>58</sup>, dihidropiridina<sup>59</sup>, diazepam<sup>60</sup> i mezenhimalnih matičnih stanica<sup>61</sup>.

## Zaključak

Depresija funkcije miokarda u sepsi i septičkom šoku, koja podrazumijeva sistoličku i/ili dijastoličku disfunkciju obje strane srca, javlja se često, dugo je poznata i intenzivno se istražuje, no nije dovoljno respektirana kao klinički entitet zbog kontroverzi kojima je okružena. Složene je i nedovoljno razjašnjene patogeneze, a pojavljuje se u zahtjevnom kliničkom sindromu komplicirane sepse koji je visokog mortaliteta i brze dinamike. Dijagnoza se postavlja najlakše ehokardiografski, no to zahtijeva primjerenu educiranost i tehničku podršku. Ne postoji specifično liječenje već ono za sepsu uz hemodinamsku podršku, iako su u istraživanjima mnogi mogući kardioprotektivi. Sve to čini srčanu disfunkciju u sepsi još uvijek velikom nepoznanicom koju dodatna istraživanja trebaju rasvijetliti radi poboljšanja prevencije, dijagnostičkoga procesa i osiguranja specifičnoga kardioprotektivnoga liječenja i boljeg ishoda.

tive oral and digestive decontamination, hydrocortisone, transfusion of erythrocytes and mechanical ventilation, sedation, analgesia, neuromuscular blocking, prophylaxis of deep arterial thrombosis, H2 blockers, proton pump inhibitors and dialysis<sup>3</sup>.

Apart from the abovementioned therapeutical options, there are also others, either more focused on sepsis or on the direct improvement of the cardiac function in sepsis, which are already in use, but are not contained in the guidelines or are in the experimental phase. Levosimendan is a vasodilator with a positive inotropic effect which increases the sensitivity of contractile myofilaments to calcium and leads to the improvement of cardiac function in patients with septic shock<sup>56</sup>. The protective effect of blockers of beta receptors<sup>57</sup>, statins<sup>58</sup>, dihydropyridines<sup>59</sup>, diazepam<sup>60</sup>, and mesenchymal stem cells<sup>61</sup> is still being researched.

## Conclusion

The depression of the myocardial function in sepsis and septic shock with the systolic and/or the diastolic dysfunction of both sides of the heart is very common. It has been known for a long time and is being intensively researched, but is not generally accepted as a clinical entity due to the surrounding controversies. It has a complex and insufficiently researched pathogenesis, and occurs in the clinical syndrome of complicated sepsis which has a high mortality rate and a rapid dynamic. The easiest way to achieve a diagnosis is by using an echocardiogram, which demands suitable training and technical support. There is no specific treatment, apart from the one for sepsis with hemodynamic support, although many cardioprotectives are currently being investigated. Cardiac dysfunction in sepsis remains unclear, and further research should clarify it in order to improve the prevention, the diagnostic process, and the defining of specific cardioprotective treatment, as well as increase the chances for better outcomes.

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