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How Immediate Decisions Save Lives – The Latest Practices and Studies in Emergency Medicine.

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ABOUT JOURNAL

Aim and scope

Annales Medicinae Urgentis (AMU) is a open-access peer reviewed medical journal published by the Croatian Society for Emergency Medicine that aims to improve the care of patients with emergency and critical illness by acquiring, discussing, distributing, and promoting evidence-based information relevant to emergency physicians and intensivists.

It publishes original original articles, reviews, case reports, meta-analysis, comments, methodologies, perspectives/ viewpoints, editorials, images, news, communications, letters to the editor, etc with no restrictions on the maximum length of manuscripts, provided that the text is concise and comprehensive. The AMU uses the Diamond Open Access model. This means that there are NO author processing fees and no fees to access the published papers.

HLZ - HRVATSKO DRUŠTVO ZA HITNU MEDICINU
CMA - CROATIAN SOCIETY OF EMERGENCY MEDICINE

CONTENT

ANNALES MEDICINAE URGENTIS: *MESSAGE FROM THE EDITORS*

Prof. Višnja Nesek Adam, MD, PhD

Prof. Ivan Gornik, MD, PhD

Dear Colleagues,

It is with great excitement and heartfelt gratitude that we present to you the inaugural issue of Annales Medicinae Urgentis, the official open-access, peer-reviewed journal of the Croatian Medical Association - Croatian Society of Emergency Medicine (CMA - CSEM). As the editors of this new journal, we are thrilled to be part of this important project, which marks a significant step in the ongoing development of our Society and the field of emergency and critical care medicine.

This journal is the natural continuation of our collective efforts to improve patient care in emergency and critical situations. By providing a platform for sharing evidencebased knowledge, clinical experiences, and innovative ideas, Annales Medicinae Urgentis will serve as a space where emergency physicians, intensivists, and healthcare professionals from diverse disciplines can come together to learn, collaborate, and grow.

Our mission is to create a journal that reflects the best of our profession—one that promotes the exchange of ideas, encourages scientific discussion, and fosters a community of practice that will ultimately improve patient outcomes. We aim to publish a wide variety of articles, including original research, reviews, case reports, meta-analyses, editorials, and more. We are committed to maintaining high scientific standards, but we also want to keep the journal accessible and relevant to all Prof. Višnja Nesek Adam, MD, PhD Prof. Ivan Gornik, MD, PhD healthcare professionals working in emergency and intensive care settings.

We strongly believe that Annales Medicinae Urgentis can grow into a respected and essential publication, but it will only do so with the active support and involvement of all of you—our colleagues, mentors, and experts in the field. We encourage you to submit your work, share your expertise, and engage in the collaborative process of building this journal into something meaningful for our profession.

We would like to express our deepest thanks to everyone who has contributed to this first issue. To the authors of the inaugural articles: your dedication and trust have laid the groundwork for what we hope will become a valuable resource for many years to come. To the reviewers: your time, effort, and invaluable feedback have ensured the quality of this journal, and we are deeply appreciative.

Looking ahead, we are excited about the future of Annales Medicinae Urgentis. As we expand our editorial team and bring in new collaborators, we will work tirelessly to ensure that this journal continues to grow in both its content and its impact. Our ultimate goal is to achieve indexing and international recognition as soon as possible, and we are confident that with your support, we can achieve this and further elevate the standing of our profession on the global stage.

Starting this journal is a big step forward for the Croatian Society of Emergency Medicine, and we are excited to see where it will take us. We know that the path to success requires hard work, dedication, and collaboration, but we are confident that with all of your help, Annales Medicinae Urgentis will thrive and become an essential resource for emergency and critical care professionals everywhere. We are committed to making this journal a recognized and indexed publication within the global medical community, and we believe that together, we can achieve this important goal.

Thank you for your contributions, your trust, and your belief in this project. Together, we can build a journal that will serve as a strong voice for our profession and contribute to the ongoing improvement of patient care in critical situations.

Warm regards,

Prof. Višnja Nesek Adam, MD, PhD
and *Prof. Ivan Gornik, MD,PhD*
Editors-in-Chief, Annales Medicinae Urgentis

REVIEW ARTICLE / PREGLEDNI ČLANAK

ENDOVASCULAR MANAGEMENT OF NON-VARICEAL GASTROINTESTINAL BLEEDING

ENDOVASKULARNO LIJEČENJE NEVARIKOZNOG GASTROINTESTINALNOG KRVARENJA

*** Ana Marija Alduk[1,2], Elvira Krešić[1], Ivana Jurca[1], Ivan Gornik[2,3]**

Abstract

Gastrointestinal bleeding is a common and potentially life-threatening condition that requires prompt diagnosis and management. Most cases respond well to conservative treatments and endoscopic therapies. However, there is a subset of patients with significant bleeding for whom these methods are ineffective, necessitating endovascular treatment. Endovascular therapy has become the preferred option over open surgery due to its advantages, most importantly reduced morbidity and mortality. This review outlines the indications for endovascular management of gastrointestinal bleeding, with a focus on critical considerations in emergency medicine such as patient selection, hemodynamic instability, and anatomical challenges. It also discusses the role of imaging in identifying candidates for intervention and provides an overview of procedural approaches and outcomes.

Key words: gastrointestinal bleeding; endovascular therapy; embolization

Sažetak

Gastrointestinalno krvarenje je često i potencijalno po život opasno stanje koje zahtijeva brzu dijagnostičku obradu i liječenje. Većina slučajeva dobro odgovara na konzervativno liječenje i endoskopske zahvate. Međutim, kod određene skupine pacijenata sa značajnim krvarenjem ove metode su neučinkovite, te je kod njih potrebno endovaskularno liječenje. Endovaskularno liječenje je bolja opcija od kirurškog zahvata zbog manjeg morbiditeta i mortaliteta. Prikazat ćemo indikacije za endovaskularno liječenje gastrointestinalnog krvarenja, s naglaskom na ključne aspekte u hitnoj medicini, kao što su selekcija pacijenata, hemodinamska nestabilnost i anatomski izazovi. Važna je i uloga slikovne dijagnostike u identificiranju kandidata za endovaskularnu intervenciju.

Ključne riječi: gastrointestinalno krvarenje; endovaskularno liječenje; embolizacija

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Introduction

Non-variceal gastrointestinal bleeding (GIB) is a frequent cause of hospital admission. It can be broadly classified into two groups according to its relationship to the ligament of Treitz: upper and lower GIB.

The clinically apparent GIB as visible blood loss may manifest as hematemesis, melena, or hematochezia. Hematemesis refers to vomiting red blood or coffee-ground emesis and suggests bleeding proximal to the ligament of Treitz. Melena is defined as black, tarry stool that occurs several hours after the bleeding event and results from the degradation of blood to hematin or other hemochromes by gut bacteria and can be seen with variable degrees of blood loss, being visible with as little as 50 mL of blood. Hematochezia refers to red or maroon blood in the stool and suggests active bleeding, usually from the lower GIB. It can also be seen in the massive upper GIB, typically associated with hemodynamic instability (1). Types of GIB's are shown in Table 1.

Differentiating upper and lower GIB based on the clinical presentation of hematemesis, hematochezia, or melena may be difficult and unreliable. Patients with upper GIB commonly present with hematemesis and/or melena, although those with a brisk upper gastrointestinal (GI) source can present with hematochezia. In 70 % of cases, GIBs are located in the upper GI tract (2,3). With an incidence of 50 to 100 per 100 000 population, it is a common pathology with a median patient age of 60–70 years (4). In 70–75 % of cases an upper GIB ceases spontaneously. The mortality rate is between 3 and 14% and for intensive care patients between 42 and 64 % (2). In approximately 50% of cases, upper GIB results from an ulcer disease such as a gastric ulcer or duodenal ulcer. Other causes include tumour bleeding, Mallory-Weiss syndrome, erosive gastritis or duodenitis, reflux esophagitis, angiodysplasia and iatrogenic or post-traumatic changes. A special cause of upper GIB is acute bleeding of the peripancreatic vessel branches, which is often the result of pancreatitis, surgery, tumours or trauma.

Lower GIB causes approximately 30 % of all GIB, with an incidence of about 20 to 30 per 100 000 population and a median age of 65–80 years, increasing dramatically with age (5). In 80–85 % of cases lower GIB ceases spontaneously. Recent studies indicate the mortality between 2 and 5 % (2). The most common cause of lower GIB is diverticulitis and less frequent are angiodysplasia, polyps, tumours, proctitis or chronic inflammatory bowel disease (6). A separate group is comprised of hemorrhaging from sources outside the digestive tract, such as the biliary tract, the pancreatic duct, arterioenteric fistula, and visceral artery aneurysms or pseudoaneurysms (7).

Once the likely location of bleeding (upper, lower, or small bowel) has been determined, the list of diagnostic possibilities may be narrowed down based on the patient's history and risk factors for GIB. Important information includes the type of bleeding (overt, occult, or massive), associated signs and symptoms (e.g., abdominal pain, weight loss), contributing events (e.g., trauma, vomiting, hypotension), and recent procedures (e.g., polypectomy, liver biopsy). Key patient history and risk factors for GI bleeding are listed in Table 2.

Pretreatment imaging

Scintigraphy is the most sensitive imaging method, with the ability to detect bleeding from 0.1 ml/min (8). However, this technique is not able to define precisely the anatomic source of the bleeding. In addition, scintigraphy is too time-consuming to be used in an emergency setting. Hence, it is mainly used for intermittent bleeding.

Conventional digital subtraction angiography (DSA) is able to detect small bleeding amounts (>0.5 ml/min) (9). Its sensitivity ranges from 63 to 90 % for upper and 40 to 86 %

Table 1. Types of gastrointestinal bleedings

Type of GIB	Description
Upper GIB	GIB originating proximal to the ligament of Treitz
Lower GIB	GIB originating distal to the ligament of Treitz
Suspected small bowel bleeding	GIB in which no bleeding source is identified after performing both upper and lower endoscopy.
Overt GIB	Visible GIB such as hematemesis, hematochezia, or melena.
Massive GIB	GIB associated with hemodynamic instability (blood pressure <90 mmHg, tachycardia, symptoms of shock) or bleeding requiring transfusion of more than 4 units of packed red blood cells per 24 hours.
Obscure GIB	GIB in which no bleeding source is identified after the entire GI tract has been evaluated with advanced endoscopic and imaging techniques. Can be either overt or occult.
Occult GIB	GIB that is not clinically visible (positive fecal occult blood test or iron deficiency anemia when other causes of anemia are excluded).
Occult GIB	GIB that is not clinically visible (positive fecal occult blood test or iron deficiency anemia when other causes of anemia are excluded).

GIB – gastrointestinal bleeding; GI – gastrointestinal

Table 2. Key patient history and risk factors for gastrointestinal bleeding

Angiodysplasia	Advanced age, aortic stenosis, end-stage renal disease, anticoagulant or antiplatelet therapy
Aortoenteric fistula	Massive GIB, infectious aortitis, aortic graft, aortic aneurysm, tumor invasion, radiation injury
Bowel ischemia	Acute abdominal pain, hypotension, advanced age, embolic disease, chronic renal failure, trauma, high-risk surgery
Crohn disease	Risk factors include duration of Crohn's, perianal disease, left colon involvement, steroid use
Delayed postpolypectomy bleeding	Polyp size > 10 mm, thick stalk, anticoagulant or antiplatelet therapy
Dieulafoy lesion	Antiplatelet therapy, alcohol abuse, NSAID
Diverticular bleeding	Painless hematochezia, advanced age, hypertension, anticoagulant therapy, NSAID
GI malignancy	Unexplained weight loss, change in bowel habits, anemia
Hemobilia	Liver biopsy, cholecystectomy, endoscopic biliary procedures, trauma, tumors, hepatic artery aneurysm
Hemosuccus pancreaticus	Pancreatitis (chronic or necrotizing), neoplasm, pseudocyst
Mallory-Weiss tear	Vomiting, often related to alcohol abuse
NSAID enteropathy or colopathy	NSAID use
Postsurgical anastomotic bleeding	Gastric bypass surgery, Billroth II, NSAID use, smoking
Peptic ulcer disease	Epigastric pain, nausea, bloating; Helicobacter pylori infection, NSAID, anticoagulant or antiplatelet therapy, stress, Zollinger-Ellison syndrome
Varices and portal hypertensive gastropathy	Massive GIB; cirrhosis, portal hypertension, portal vein thrombosis

GIB – gastrointestinal bleeding; GI – gastrointestinal; NSAID – non-steroidal anti-inflammatory drug

for lower GI tract (10). The localization of bleeding can be improved by previous placement of metal clips at the bleeding source during endoscopy.

Contrast enhanced computerized tomography is the imaging method of choice: it is noninvasive, fast, and more sensitive than digital subtraction angiography (DSA).

Contrast enhanced computerized tomography (CECT) can detect even smaller amounts of bleeding (<0.3 ml/min), and is more sensitive than DSA (10). In addition, compared to DSA, it is able to depict surrounding anatomical structures and to determine not only the place, but also a possible cause of bleeding. Since GIBs are usually intermittent in nature, it is important to scan the patients during the actual bleeding in order to determine the bleeding localization. CECT also displays the complete vascular anatomy and allows planning of subsequent endovascular intervention. Oral contrast should not be administered, because it will mask the intraluminal contrast material, which is a radiological sign of bleeding. Even in hemodynamically unstable patients with acute significant bleeding of obscure localization, CECT should be considered the imaging method of choice due to its non-invasiveness, speed, and sensitivity. Since the CECT is more sensitive than DSA, DSA and embolization should be considered only in cases when bleeding is identified on CECT.

Indications for endovascular treatment

The indication for endovascular treatment is usually based on a multidisciplinary consensus between the gastroenterologist, radiologist, and surgeon. In the event of acute significant gastrointestinal bleeding and after the failure of conservative treatment, endoscopy is the method of choice. Acute significant bleeding is generally considered as bleeding requiring transfusion of at least 4 units of blood within 24h or causing signs of hemodynamic instability and shock (systolic blood pressure <100, tachycardia >100) (11). Endovascular treatment is indicated for patients with significant acute GIB with endoscopically untreatable or unrevealed source of bleeding or with excessive bleeding that obscures the endoscopic view (7). It is recommended to perform CECT before the intervention. In the case of a negative CECT, the probability of detection of the bleeding site in DSA is low. Surgical treatment is generally considered in operable patients, especially those with a bleeding gastroduodenal peptic ulcer (12) or recurrent bleeding from colonic diverticula (13) and after endoscopy and embolization therapy failure.

Contraindications

Contraindications for embolization in significant GIB are only relative. These include general contraindications for iodine-contrast examinations (allergy and renal insufficiency), and those of coagulopathy and residues of barium sulphate contrast agent after the previous examination.

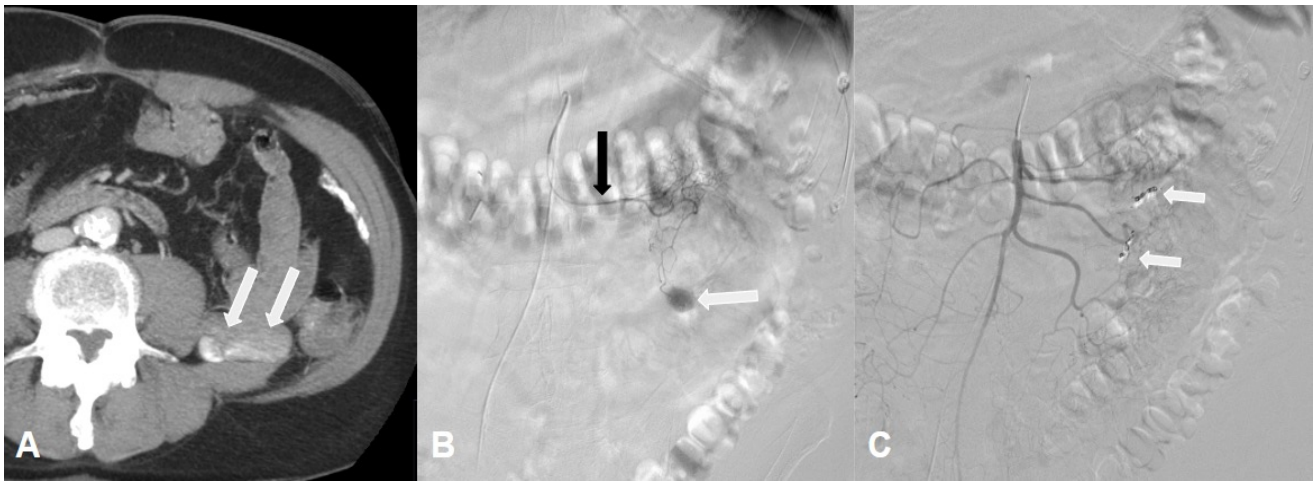

Figure 1. Lower gastrointestinal bleeding (GIB) (hematochezia) with unidentified genesis in a 74-year-old male. **A.** An axial contrast enhanced computerized tomography (CECT) shows an intraluminal contrast extravasation within a jejunal loop in the left hemiabdomen (white arrows). **B.** Superselective digital subtraction angiography (DSA) with the tip of the microcatheter in the left colic artery (black arrow) shows active bleeding (white arrow). **C.** Selective superior mesenteric artery DSA after the embolization shows two coils (white arrows) with complete cessation of the bleeding.

Procedure

Transarterial embolization (TAE) is an endovascular procedure in which embolic agents such as coils, microparticles, or liquid embolic are intentionally introduced in the vessel in order to achieve haemostasis (Figure 1).

> **Transarterial embolization is an effective procedure in the treatment of gastrointestinal bleeding in patients with bleeding source not detected on endoscopy or who cannot undergo endoscopy.**

The patient's preparation before the procedure includes supportive therapy (volume therapy, etc.) and correction of coagulopathy. Bladder catheter insertion is desirable. In patients with GI bleeding, it is necessary to have anaesthesia or intensive care physician support, particularly in unstable patients. During the procedure, blood pressure, heart rate, saturation, and ECG are monitored.

The most common access used for TAE is the common femoral artery, therefore both groins must be shaved before the procedure. The procedure is usually performed under local anesthesia with analgosedation. It is recommended that arterial puncture should be done under ultrasound guidance in order to avoid local complications. Use of spasmolytics (e.g., Buscopan) can be helpful in avoiding motion image artefacts.

The procedure begins with selective angiography to localize the source of bleeding. After verifying the source, a microcatheter is introduced coaxially through the diagnostic catheter. The most commonly used embolic materials are microcoils, PVA (polyvinyl alcohol) microspheres (500-700 um), gelatin foam, and tissue glue (Histoacryl™). Selective intraarterial infusion of vasoconstrictor agent (vasopressin) is rarely used due to the high frequency of rebleeding (>50 %) and occurrence of systemic side effects (14). It could be considered for diffuse mucosal haemorrhage, or lesions inaccessible to a microcatheter.

Due to differences in blood supply of the upper and lower GI tract, the technique of embolization also differs. The upper gastrointestinal tract is characterized by a rich network of collateral supply with a lower risk of ischemia. Before the embolization itself, it is necessary to map all the possible sources of collateral supply, especially in the region of gastroduodenal artery and pancreaticoduodenal arcades. Because of the risk of rebleeding via collaterals, it is necessary to perform embolization proximally and distally from the site of bleeding (the so-called sandwich technique). In the lower gastrointestinal tract, particularly in the colon, there is a higher portion of terminal branches. Therefore, the ischemia risk is higher, and embolization should be as selective as possible (15).

Outcomes

Generally, the morbidity and mortality associated with endovascular intervention for GIB is lower or comparable than for surgical procedure (16,17).Therefore, endovascular therapy is considered the treatment of choice for GIB following failed medical and endoscopic therapy. Predictive factors for recurrent bleeding and mortality are uncorrectable coagulopathy, older age, cirrhosis, oncologic diseases, multiple organ failure, and current corticosteroid treatment (18).

Digital subtraction angiography and embolization should be considered only in cases when bleeding is identified on contrast enhanced computerized tomography.

Complications

In addition to the standard rate of nonspecific complications associated with any angiographic procedure (such as reactions to the contrast agent, renal failure, local complications in the groin, dissection, and vasospasm), the most common and specific complication of GI embolization is ischemia. The risk of ischemia is low in the upper GI tract due to the rich collateral supply. Duodenal stenosis as a result of duodenal ischemia following embolization is rare and reported to be less than 7 %. Patients are at increased risk of ischemia if they have a previous history of surgery or radiotherapy and after embolization with glue or microparticles (11). The overall average complication rate is approximately 9 % (19). In the lower GI tract, the most common specific complication is intestinal ischemia. The mild form presented with transient abdominal pain and asymptomatic stenosis occurs in 10 % of patients. Severe ischemic complications requiring surgical treatment (symptomatic ischemic stenosis, intestinal infarction) occur in 2 % (20).

Conclusion

TAE is an effective procedure in the treatment of GIB in patients with a bleeding source not detected on endoscopy or who cannot undergo endoscopy. The clinical success and complications of this approach in upper GIB makes preventive TAE useful in selected patients due to the high risk of rebleeding, also in consideration of the generally limited complications in empirical embolization of the upper gastrointestinal tract. Patient selection should be more prudent in the treatment of lower GIB: due to poor collateral supply lower GI tract is at higher risk of ischemia, hence the treatment should be as selective as possible.

Emergency physicians must recognize the indications for endovascular intervention, prioritize rapid imaging, and facilitate timely multidisciplinary coordination to optimize patient outcomes.

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PREGLEDNI ČLANAK / REVIEW ARTICLE

SKRB O KOMPLEKSNIM BOLESNICIMA - NOVA DIMENZIJA HITNE MEDICINE

CARE FOR COMPLEX PATIENTS - A NEW DIMENSION OF EMERGENCY MEDICINE

*** Aleksandar Džakula[1], Dorja Vočanec[1]**

Sažetak

Hitna medicina definira se kao specijalnost koja se bavi prevencijom, dijagnozom i liječenjem hitnih zdravstvenih stanja u bolesnika svih dobnih skupina. Unatoč jasnim okvirima i definicijama, postavlja se pitanje sprege između tu definiranih očekivanja i stvarnosti rada hitnih medicinskih službi (HMS). S obzirom na porast starije populacije i bolesnika s kroničnim bolestima, HMS se suočava s povećanim brojem bolesnika čiji problemi nisu isključivo hitne prirode. Preopterećenje HMS-a složenim bolesnicima postaje globalni izazov, a nedostatak odgovarajuće klasifikacije i analize potreba ovih bolesnika otežava razvoj efikasnih strategija za njihovo zbrinjavanje. Predlaže se grupiranje kompleksnih bolesnika i njihovo sustavno razgraničenje u podskupine (gerijatrijski, onkološki) kako bi se olakšalo upravljanje njihovim specifičnim potrebama. Hitne medicinske službe, sa svojom otvorenom strukturom, predstavljaju ključnu točku u zdravstvenom sustavu te su pokazatelj učinkovitosti istog. Kako bi se suočile s izazovima koje donosi skrb o kompleksnim bolesnicima, HMS-i moraju razviti strategije koje će osigurati kvalitetnu skrb uz manje stresa za medicinsko osoblje. Budućnost hitne medicine leži u učinkovitom upravljanju i odgovarajućim resursima za brigu o kompleksnim bolesnicima, čime se potvrđuje njihov značaj unutar zdravstvenog sustava.

Ključne riječi: kompleksni bolesnici; hitna medicinska služba

Abstract

Emergency medicine is defined as a specialty that deals with the prevention, diagnosis and treatment of emergency medical conditions in patients of all ages. Despite clear frameworks and definitions, the question of the connection between the expectations defined therein and the reality of the work of emergency medical services (EMS) is raised. Given the increase in the elderly population and patients with chronic diseases, EMS is faced with an increasing number of patients whose problems are not exclusively emergency issue. Overcrowding of EMS with complex patients is becoming a global challenge, and the lack of adequate classification and analysis of the needs of these patients makes it difficult to develop effective strategies for their care. It is proposed to group complex patients and systematically delineate them into subgroups (geriatric, oncological) in order to facilitate the management of their specific needs. EMS, with their open structure, represent a key point in the health system and are an indicator of its efficiency. In order to face the challenges brought by the care of complex patients, EMS must develop strategies that will ensure quality care with less stress for medical staff. The future of emergency medicine lies in efficient management and adequate resources for the care of complex patients, thus confirming their importance within the healthcare system.

Key words: complex patients; emergency medical service

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Tradicionalna uloga hitne medicine

Prema definiciji europskog društva za hitnu medicinu (engl. *European Society for Emergency Medicine, EUSEM*) „*hitna medicina je primarna specijalnost uspostavljena korištenjem znanja i vještina potrebnih za prevenciju, dijagnozu i liječenje hitnih aspekata bolesti i ozljeda, koji pogađaju pacijente svih dobnih skupina s punim spektrom nediferenciranih fizičkih poremećaja i poremećaja ponašanja*" (1). U opisu poslova koje obuhvaća hitna medicina EUSEM navodi: „*Praksa hitne medicine obuhvaća bolničku i vanbolničku trijažu, resuscitaciju, početnu procjenu, telemedicinu i zbrinjavanje nediferenciranih životno ugroženih i hitnih pacijenata do otpusta ili prelaska pod skrb drugog zdravstvenog djelatnika*" (1).

Organizacijske promjene, primjena modernih tehnologija i kontinuirana edukacija omogućile su profesionalno i upravljačko osamostaljivanje jedinica za hitnu medicinu te općenito hitnih medicinskih službi.

Definicija i opis poslova jasno opisuju što radi hitna medicina te na koji način brine o bolesnicima. Međutim, postavlja se pitanje je li sagledavanje hitne medicine u tako zadanim okvirima dovoljno i možemo li iz postavljenog okvira promišljati budućnost i održivi razvoj. Drugim riječima, možemo li uskladiti očekivanja unutar struke s realitetom rada u hitnoj medicini.

Hitna medicina, u usporedbi s mnogim drugim specijalizacijama, može se smatrati jednom od mlađih grana medicine. Organizacijske promjene, primjena suvremenih tehnologija i kontinuirana edukacija omogućile su profesionalno i upravljačko osamostaljivanje jedinica za hitnu medicinu te općenito hitnih medicinskih službi. Profesionalno i organizacijsko osamostaljivanje omogućilo je stručnjacima i menadžerima ne samo da učinkovito upravljaju postojećim resursima i procesima, već i da strateški promišljaju budućnost.

Razvoj i budućnost hitnih medicinskih službi

Budućnost hitne medicine i hitnih medicinskih službi (HMS) uvelike je određena sposobnošću integracije suvremenih medicinskih tehnologija u spašavanje života i intervencije kada je u kratkom vremenskom roku potrebno pružiti optimalnu medicinsku skrb. Ta misija hitnih medicinskih službi temeljno je određenje koje će vjerojatno trajno ostati središnji stup sustava. Međutim, položaj hitne medicine u zdravstvenom sustavu, način njenog djelovanja te dostupnost otvaraju niz novih perspektiva i izazova za budući razvoj i održivost sustava HMS-a (2). Ako proširimo fokus promatranja HMS-a izvan hitnih stanja, uočavamo da se u HMS-ima pojavljuje iznimno velik broj pacijenata čiji razlog dolaska nema isključivo biomedicinsku podlogu. Naime, značajan broj bolesnika koji trebaju intervenciju HMS-a ima zdravstvena stanja povezana s neodgovarajućim funkcioniranjem zdravstvenog sustava ili s neodgovarajućim ponašanjem samih bolesnika i njihovih njegovatelja.

U okolnostima značajnog porasta starije populacije te bolesnika uključenih u programe kronične ili dugotrajne terapije, broj ovakvih bolesnikau HMS-ima kontinuirano raste. Drugim riječima, utjecaj ne-biomedicinskih čimbenika na rad HMS-a postaje sve značajniji i dio je trenda koji se neprekidno povećava.

Značajan broj bolesnika koji trebaju intervenciju hitne medicinske službe ima zdravstvena stanja povezana s neodgovarajućim funkcioniranjem zdravstvenog sustava ili s neodgovarajućim ponašanjem samih bolesnika i njihovih njegovatelja.

Problem preopterećenja hitnih medicinskih službi

Problem preopterećenja HMS-a bolesnicima koji imaju složena, ali ne nužno i hitna stanja, ističe se kao jedan od ključnih prioriteta u većini razvijenih zemalja, jer sve dijele iste trendove porasta broja starijeg stanovništva te bolesnika koji trebaju dugotrajne i medicinske intenzivne intervencije (3,4). Međutim, analiza ovakvih stanja i mogućnosti njihova rješavanja nije jednostavna, a posebno je izazovno provesti usporedbu uzroka problema i mogućih intervencija (5). Naime, osim što se socijalne okolnosti i odnosi razlikuju među državama i zajednicama, značajne su i razlike u organizaciji zdravstvenih sustava te u protokolima po kojima postupaju izvanbolničke i bolničke službe. Ove razlike mogu značajno utjecati na pristup i rješavanje problema HMS-a.

Unatoč činjenici da problem opterećenja HMS-a bolesnicima s kompleksnim potrebama ostaje konstantan i globalno prisutan, on je još uvijek nedovoljno analiziran i obrađen. Riječ je o zajedničkom izazovu za medicinske službe diljem svijeta. Dodatni problem u raspravama o ovom izazovu zdravstvenih službi predstavlja upotreba različitih, često nedovoljno definiranih termina kojima se opisuju bolesnici sa složenim i zahtjevnim potrebama. Koriste se izrazi poput teški bolesnici, kompleksni bolesnici, bolesnici s pridruženim bolestima, bolesnici koji često koriste zdravstvene usluge ili oni koji troše znatne resurse sustava.

Međutim, unutar ovog širokog skupa bolesnika nisu sustavno razgraničene njihove specifične potrebe, razlozi kontinuiranog rasta tih potreba niti mogućnosti za intervencije. Nedostatak jasnih definicija i klasifikacija

otežava razumijevanje problema i razvoj ciljanih strategija za njihovo rješavanje.

Problem koji nema pravo ime

Nedostatak odgovarajuće klasifikacije i analize potreba ovih bolesnika zapravo nije iznenađujući, jer prema temeljnoj definiciji hitne medicine, oni nisu, niti bi trebali biti, prioritet HMS-a. Moglo bi se reći, ipak, da su se ti bolesnici na neki način "dogodili" hitnoj medicinskoj službi tijekom njenog procesa razvoja i osamostaljivanja od drugih dijelova zdravstvenog sustava. Danas su bolesnici sa složenim potrebama postali značajan teret za hitnu medicinu te su se nametnuli kao prioritet za organizacijsko i stručno rješavanje.

Problemi neodgovarajućeg funkcioniranja zdravstvene zaštite ili preopterećenja sustava najčešće se primarno analiziraju kroz financijske pokazatelje (6). Poslovanje zdravstvenih ustanova često je izravno pod utjecajem načina na koji zdravstvene službe funkcioniraju, odnosno koliko su učinkovite. U slučaju hitne medicinske službe, posebna se pažnja posvećuje skupini bolesnika poznatih kao "high utilizers" – bolesnici koji koriste usluge HMS-a više puta tijekom jedne godine (7,8). Takva definicija omogućuje relativno jednostavno prepoznavanje, praćenje i analizu troškova koje generira svaki bolesnika iz ove skupine. Također, moguće je pratiti što se događa s tim bolesnicima izvan bolničkog sustava, ali to je često ograničeno na dostupnost podataka o svim ostalim pokazateljima zdravstvenog stanja i skrbi koju bolesnik prima izvan bolnice. Zbog svega navedenog, skupina bolesnika "high utilizers" može poslužiti kao dobar početak ili pokazatelj preopterećenja hitnih službi, ali i šireg problema koji vjerojatno postoji u drugim segmentima zdravstvenog sustava (9,10).

Kompleksan problem i/ili kompleksni bolesnici

Mogući smjer u rješavanju ovog problema mogao bi biti grupiranje svih ovih bolesnika u jedinstvenu kategoriju kompleksnih bolesnika, koju bi potom trebalo sustavno klasificirati i organizirati u podskupine. Klasifikacija bi trebala uzeti u obzir razloge njihove kompleksnosti, dionike s kojima su primarno povezani u zdravstvenom sustavu te ulogu hitnih medicinskih službi u zbrinjavanju svake od tih specifičnih skupina.

Primjeri takvih specifičnih skupina kompleksnih bolesnika uključuju:

- bolesnike koji trebaju potporu medicinskih tehnologija i aparata izvan bolničkog okruženja (npr. kod kuće);
- bolesnike kojima je potrebna palijativna skrb;
- bolesnike s demencijom ili problemima mentalnog zdravlja;
- bolesnike u složenim socijalnim okolnostima, bilo unutar vlastite obitelji, udomiteljstva, ili druge zajednice u kojoj žive.

Ovakav pristup omogućio bi ciljano planiranje i učinkovitije upravljanje potrebama kompleksnih bolesnika unutar sustava HMS-a.

Pokušaji rješavanja problema ove skupine bolesnika već se mogu prepoznati kroz neke organizacijske prijedloge i promjene u različitim državama. Međutim, unutar tih promjena moguće je uočiti i nedostatak sustavnog promatranja kompleksnosti potreba bolesnika, što nosi rizik da predložene organizacijske promjene i intervencije neće biti učinkovite.

Na primjer, sustavi subspecijalizacija ili specifičnih edukacija u Sjedinjenim Američkim Državama pokazuju kako HMS nije samo medicinska, već i društvena točka sustava, koja osim ključne medicinske uloge ima i ulogu prozora prema zajednicama. U takvim zajednicama hitne službe često se suočavaju s problemima siromaštva, nasilja i drugim izazovima koji više pripadaju sferi javnog zdravstva nego kliničke medicine.

> **Problem preopterećenja HMS-a bolesnicima koji imaju složena, ali ne nužno i hitna stanja, ističe se kao jedan od ključnih prioriteta u većini razvijenih zemalja, jer sve dijele iste trendove porasta broja starijeg stanovništva te bolesnika koji trebaju dugotrajne i medicinske intenzivne intervencije.**

S druge strane, neke zdravstvene ustanove pokušavaju fokusirati svoje usluge na specifične skupine kompleksnih pacijenata. Tako se predlažu i uvode hitne medicinske službe specijalizirane za onkologiju, gerijatriju ili druge specifične skupine, pozivajući se pritom na postojeća iskustva specijaliziranih hitnih službi za djecu unutar pedijatrijskih odjela (11).

Manjak potpore u zajednici, nedovoljno obrazovanje njegovatelja te propusti u izvanbolničkom zbrinjavanju kompleksnih pacijenata, hitne medicinske službe u Velikoj Britaniji pokušavaju rješavati osnaživanjem laika i profesionalaca koji brinu o tim bolesnicima izvan zdravstvenih ustanova. Ovaj pristup temelji se na postojećim mrežama primarne zdravstvene zaštite i javne zdravstvene službe te prepoznaje ključnu ulogu HMS-a u prevenciji hospitalizacija, olakšanju procesa otpuštanja pacijenata iz bolnice i općenito racionalnijem korištenju hitne medicinske službe i drugih složenih oblika zdravstvene zaštite (12,13).

Hitna medicinska služba kao indikator učinkovitosti sustava

Bez obzira na način promatranja HMS-a i na zdravstveni sustav u kojem djeluju, očito je da je budućnost rada

hitnih medicinskih službi u značajnoj mjeri određena zbrinjavanjem kompleksnih bolesnika. Hitne medicinske službe, zbog svoje pozicije i relativno slobodnog pristupa, ostaju trajno otvorena vrata za sve skupine bolesnika s nezadovoljenim potrebama. Bolesnici s kompleksnim potrebama, zbog svoje složene zdravstvene situacije i međusobnog negativnog utjecaja njihovih stanja, često će završiti u hitnoj medicinskoj službi, osobito u bolničkom okruženju.

Iako se hitne medicinske službe obično promatraju kao mjesto ulaska bolesnika u bolnice i općenito u zdravstveni sustav, one su istovremeno i pokazatelj učinkovitosti načina na koji bolesnici izlaze iz zdravstvenog sustava ili ih se pokušava otpustiti iz njega. Konkretno, bolesnici koji nisu odgovarajuće zbrinuti nakon izlaska iz bolnice svoj će zahtjev za zdravstvenom zaštitom i pomoć najprije ponovno usmjeriti prema HMS-u.

Zbog toga je osovina i koordinacija između rada hitnih medicinskih službi i službi za otpust bolesnika od presudne važnosti za održivost bolničke hitne službe. Naime, svaki bolesnik koji nije odgovarajuće otpušten iz bolnice vjerojatno će se u roku od nekoliko sati ili dana vratiti na hitni bolnički prijem, ali u znatno težem i složenijem stanju nego što je bio pri otpustu. Pri takvom povratku, bolesnik se često neće susresti s liječnikom koji je bio upoznat s njegovim stanjem i tijekovima liječenja, već s mladim i često neiskusnim liječnikom koji je preopterećen ostalim bolesnicima na hitnom bolničkom prijemu. Takve situacije dodatno pogoršavaju stanje bolesnika i opterećenje sustava.

Umjesto zaključka

Kompleksni bolesnici definitivno nisu bili prioritet u razvoju hitne medicine i organizaciji hitnih medicinskih službi, ali su postali realitet. Iako se rad s kompleksnim bolesnicima rijetko doživljava s entuzijazmom, činjenica je da njihov broj svakodnevno raste, a njihove potrebe postaju sve zahtjevnije. To ih kontinuirano vraća u fokus zdravstvenog sustava, a posebno hitnih medicinskih službi.

Stoga je u planiranju budućih edukacija i organizacije sustava nužno osigurati odgovarajuće kompetencije i resurse kako bi se hitne medicinske službe mogle učinkovito, a uz najmanje stresa, brinuti za kompleksne bolesnike. To jednostavno postaje nova stvarnost hitne medicine i obaveza onih koji sustav planiraju i razvijaju.

Unatoč činjenici da problem opterećenja HMS-a bolesnicima s kompleksnim potrebama ostaje konstantan i globalno prisutan, on je još uvijek nedovoljno analiziran i obrađen.

Demografske, socijalne i organizacijske promjene jasno ukazuju na to da skrb o kompleksnim bolesnicima mora postati prioritet. Sustav hitne medicine mora pronaći odgovarajuće odgovore na te izazove. Taj odgovor ne mora značiti preuzimanje pune odgovornosti za ovu skupinu bolesnika niti potpuno usmjeravanje cijelog sustava hitne medicine prema njima. Međutim, mora biti dovoljno promišljen i odlučan kako bi se bolesnicima osigurala minimalna, ali kvalitetna skrb, a profesionalcima u hitnim medicinskim službama uvjeti za siguran i zadovoljavajući rad. Rad bez nepotrebnog stresa i straha od vrste ili broja kompleksnih bolesnika koji će se neke noći ili vikenda "pojaviti baš u mojoj smjeni".

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REVIEW ARTICLE / PREGLEDNI ČLANAK

APPLICATION OF NONINVASIVE VENTILATION IN EMERGENCY MEDICINE: CURRENT STRATEGIES AND CHALLENGES

PRIMJENA NEINVAZIVNE VENTILACIJE U HITNOJ MEDICINI: AKTUALNE STRATEGIJE I IZAZOVI

*** Šitum Ivan[1], Erceg Ante[1], Lovrić Daniel[2]**

Abstract

Noninvasive ventilation (NIV) has become a key method in emergency medicine for the management of acute respiratory failure (ARF) and is often one of the most critical scenarios in emergency settings. This paper reviews the latest noninvasive ventilation strategies, including high-flow nasal cannula (HFNC) and noninvasive positive airway pressure (CPAP, BiPAP), and their effectiveness in emergency medical settings. It also discusses the use of NIV in various emergencies including cardiogenic pulmonary edema, acute exacerbation of chronic obstructive pulmonary disease (COPD), and hypoxemic respiratory failure. Finally, this paper reviews the challenges in implementing noninvasive ventilation in emergencies and its advantages compared to invasive approaches.

Keywords: noninvasive ventilation; emergency medicine; acute respiratory failure

Sažetak

Neinvazivna ventilacija (NIV) postala je ključna metoda za liječenje akutnog respiracijskog zatajenja u hitnoj medicini i često je jedan od najkritičnijih scenarija u hitnim slučajevima. Ovaj rad daje pregled najnovijih strategija neinvazivne ventilacije, uključujući nosnu kanilu visokog protoka (HFNC) i neinvazivni pozitivni tlak u dišnim putovima (CPAP, BiPAP), i njihovu učinkovitost u hitnim medicinskim uvjetima. Također se raspravlja o upotrebi NIV-a u različitim hitnim slučajevima uključujući kardiogeni plućni edem, akutnu egzacerbaciju kronične opstrukcijske plućne bolesti (KOPB) i hipoksemično respiracijsko zatajenje. Na kraju, ovaj rad daje pregled izazova u primjeni neinvazivne ventilacije u hitnim slučajevima i njezinih prednosti u usporedbi s invazivnim pristupima.

Ključne riječi: neinvazivna ventilacija; hitna medicina; akutno respiracijsko zatajenje

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Introduction

Acute respiratory failure (ARF) is one of the most urgent and demanding situations in emergency medicine and often requires rapid and effective therapy to avoid further complications and mortality (1). Traditional methods of invasive ventilation, such as endotracheal intubation and mechanical ventilation, are associated with an increased risk of complications, such as infections, barotrauma, and prolonged hospitalization (2). Non-invasive ventilation strategies have recently become increasingly important because of their effectiveness in avoiding these complications and improving patient outcomes. Noninvasive ventilation (NIV), including high-flow nasal cannula (HFNC), continuous positive airway pressure (CPAP), and bilevel positive airway pressure (BiPAP), is increasingly used in emergency settings to manage patients with acute respiratory failure. However, they are also not without risks (3). The approach to treating ARF is stepwise and includes a gradual increase in support from a nasal catheter, through HFNC and NIV, to invasive mechanical ventilation (IMV), a device for extracorporeal CO2 removal ($ECCO_2R$), and a device for extracorporeal membrane oxygenation (ECMO) (Fig 1) (1). Some patients may need to be transferred to intensive care units for escalated respiratory support after the initial respiratory support is initiated in emergency medicine departments. However, some patients can be thoroughly cared for in emergency medicine departments if the problem is identified in time and if they are adequately cared for using the correct respiratory support modality (4).

This study aims to analyze the existing strategies for applying NIV in emergency medicine, investigate the advantages and limitations of these methods, and discuss their applications in different emergency scenarios. In addition, the benefits of non-invasive versus invasive methods were compared, including improved mortality and reduced need for intubation.

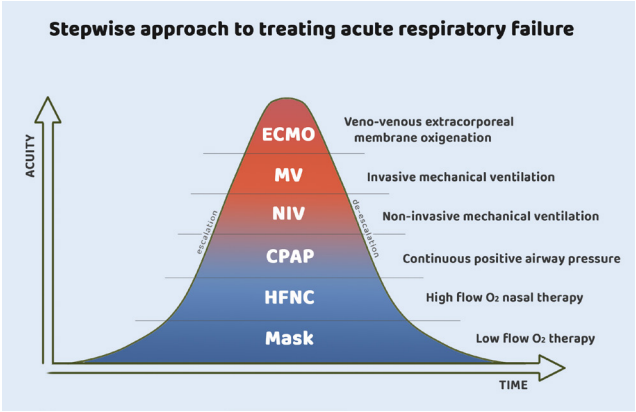

Figure 1. Stepwise approach to treating acute respiratory failure

Potential applications of noninvasive ventilation in emergency medicine

In emergency medicine, rapid intervention and appropriate airway management are essential for the successful management of patients with acute respiratory failure. ARF can be caused by various conditions, including acute exacerbation of chronic obstructive pulmonary disease (COPD), cardiogenic pulmonary edema, hypoxemic respiratory failure, and infectious diseases such as pneumonia or sepsis (4,5).

Traditionally, invasive ventilation has been the first-line therapy for these patients; however, because of the risks associated with endotracheal intubation, noninvasive methods are increasingly preferred. The main advantages of NIV in emergencies include reducing the need for endotracheal intubation, reducing the risk of nosocomial infections, improving patient comfort, facilitating breathing without sedation, and accelerating recovery time (4).

In emergency settings, noninvasive methods are often used in patients with cardiogenic pulmonary edema or COPD because they allow rapid stabilization without requiring intubation, which is more effective in specific patient groups (6,7).

Strategies for the management of acute respiratory failure

The most commonly used noninvasive strategies for patients with acute respiratory failure include CPAP, BiPAP, and HFNC. These methods provide respiratory support, improve the ventilation-perfusion ratio, and reduce the workload on the lungs and heart.

> Non-invasive ventilation, including HFNC, CPAP, and BiPAP, is increasingly favored in managing acute respiratory failure due to its ability to reduce the need for intubation, lower infection risks, and improve patient outcomes in emergency settings.

Continuous positive airway pressure (CPAP)

CPAP provides a constant positive airway pressure, prevents alveolar collapse, and allows better oxygenation. This method is beneficial for patients with cardiogenic pulmonary edema and acute exacerbations of COPD. Studies have shown that CPAP reduces the need for intubation and reduces mortality in patients with acute respiratory failure in emergency settings (8).

Bilevel-positive airway pressure (BiPAP)

BiPAP induces pressure changes during inspiration and expiration, further facilitating breathing in patients with hypercapnia, such as those with COPD. In emergency

settings, BiPAP is often used as first-line therapy for patients with exacerbations of chronic lung diseases (9).

High-flow nasal cannula (HFNC)

HFNC is a relatively new technology that delivers warm and humidified oxygen at high flow rates through the nasal cannula. Studies have shown that HFNC may be an effective alternative for patients with hypoxemic respiratory failure, especially when standard oxygen therapy is insufficient. HFNC also has an advantage over CPAP and BiPAP in terms of greater patient comfort and a reduced risk of side effects (10).

Noninvasive Negative Pressure Ventilation (NPV)

Negative ventilation involves the creation of negative pressure around the chest and abdomen to allow lung expansion during inspiration, as opposed to positive ventilation, in which air is actively forced into the lungs by positive pressure. Historically, NPV was popular in treating poliomyelitis with devices such as the "iron lung," but its use in acute and chronic respiratory failure has been re-examined.

Recent research has shown that NPV can be used in patients with hypercapnic respiratory failure, especially in combination with a high-flow nasal cannula (HFNC). This combination improves respiratory function without the need for invasive ventilation. For example, Imitazione et al. (2021) described a patient with acute respiratory failure and muscular dystrophy in whom they combined NPV and HFNC and noted significant improvements in respiratory parameters without the need for invasive ventilation (11).

Additionally, NPV has gained renewed attention during the COVID-19 pandemic, when combinations of various non-invasive methods, including NPV, have been shown to reduce hypoxia and improve respiratory mechanics. Chandrasekaran and Monikandan (2022) highlighted the importance of NPV in combination with an oxygen mask during the treatment of COVID-19 patients, leading to positive clinical outcomes (12). Although NPV is not as widely used as other methods, research suggests the potential utility of this method in emergency medicine, particularly in patients with chronic lung disease and severe respiratory failure.

Noninvasive ventilation in emergency medicine

In emergency medical settings, the rapid use of non-invasive ventilation can significantly improve outcomes in patients with acute respiratory failure. Non-invasive ventilation methods, such as CPAP and BiPAP, can be used in prehospital settings, allowing for earlier stabilization of patients. In hospital settings, using NIV in emergency departments has reduced mortality, the need for intubation, and intensive care unit stays (11). Given these general advantages, NIV specific applications in conditions such as cardiogenic pulmonary edema and COPD exacerbations demonstrate its critical role in emergency medicine.

While non-invasive ventilation offers significant benefits, its use in emergency medicine is challenging due to the need for rapid decision-making and proper staff training. Timely identification of patients who will benefit from NIV and exploring combination therapies, such as HFNC with BiPAP, remain critical areas for improving outcomes.

Use of NIV in acute COPD exacerbations

COPD is one of the most common causes of respiratory failure in the emergency setting. NIV, especially BiPAP, is key to managing these patients, as it helps reduce hypercapnia and facilitates breathing. According to a meta-analysis by Sakuraya et al. (2021), the use of NIV reduced the risk of intubation in patients with COPD by 75% (7).

Cardiogenic pulmonary edema

CPAP is particularly beneficial in patients with cardiogenic pulmonary edema because it helps to reduce cardiac preload and afterload, thereby improving cardiac function and facilitating breathing. This method can significantly reduce the risk of invasive ventilation in patients with acute heart failure (13).

Hypoxemic respiratory failure

HFNC is increasingly used in patients with hypoxemic respiratory failure, especially in those who are not candidates for intubation. HFNC allows for better oxygenation with greater patient comfort, a key advantage in emergencies (12). In comparison, our study showed that the use of high levels of positive end-expiratory pressure (PEEP) via noninvasive ventilation is safe and effective in patients with COVID-19-associated acute respiratory distress syndrome (ARDS) (14). The effectiveness of this method is evident in the early stages of treatment, where the use of NIV avoids intubation in most patients, with a reduction in mortality among patients who remain on NIV (8).

Monitoring of the application of non-invasive mechanical ventilation

It is vital to closely monitor patients' vital and respiratory parameters during non-invasive mechanical ventilation. This can be a challenge for the busy bustle of the emergency department. Timely recognition of inadequate respiratory support (NIV failure) prevents postponement of imminent intubation, which is associated with worse clinical outcomes (15). Many scores have been obtained for this purpose. One such score is HACOR, which has proven to be an excellent predictive tool for NIV failure (2,14,16).

Discussion

Although non-invasive ventilation has significant advantages, its implementation in emergency medicine is challenging. The need for rapid patient evaluation and decision-making regarding an appropriate ventilation strategy can be challenging, particularly in patients with mixed forms of respiratory failure.

One of the key challenges is the timely identification of patients who will benefit from noninvasive ventilation without missing the point when invasive ventilation is required. In addition, adequate training of the medical staff in the proper use and monitoring of patients on NIV is necessary, as improper use can lead to deterioration of the condition and the need for invasive ventilation.

Studies have shown that combining different noninvasive methods, such as HFNC and BiPAP, is effective in certain patients, especially during the COVID-19 pandemic when respiratory symptoms and failure are more pronounced (2). More research is needed to better understand the effects of combination therapies and their long-term effectiveness in emergency settings.

Conclusion

Noninvasive ventilation is a key emergency medicine method for treating patients with acute respiratory failure. Its advantages include a reduced risk of invasive complications and improved patient comfort, making it the preferred approach in many emergencies. However, careful evaluation of patients and appropriate training of the medical staff are required to maximize the benefits of this method. With further research and technological improvements, noninvasive ventilation methods will play an increasingly important role in emergency medicine.

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PREGLEDNI ČLANAK / REVIEW ARTICLE

UPOTREBA KETAMINA U HITNIM STANJIMA

KETAMINE USE IN EMERGENCY SETTINGS

*** Tamara Murselović[1,2], Višnja Nesek Adam[1,2,3,4], Sanja Berić[1,2]**

Sažetak

Ketamin je fenciklidinski derivat (*N*-1-fenil-cikloheksilpiperidin-), anestetik s disocijativnim, analgetskim i psihodeličnim svojstvima, široko korišten u humanoj i veterinarskoj medicini. U upotrebi je od 1964 godine. Zbog njegovih halucinogenih svostava 70-tih godina prošlog stoljeća započinje njegova nemedicinska upotreba kao rekreacijske droge. Ketamin primarno djeluje kao nekompetitivni agonist N-metil-D-aspartat (NMDA) receptora. Svojim djelovanjem izaziva snažnu anesteziju, sedaciju i amneziju istovremeno održavajući spontano disanje. Upotreba ketamina danas je široka, osim kao anestetik koristi se za liječenje kronične boli, te kao brzodjelujući antidepresiv. Ovaj pregledni članak ima cilj pružiti kratki prikaz svestrane upotrebe ketamina s naglaskom na njegovo korištenje u hitnim stanjima.

Ključne riječi: ketamin; anestezija; intubacija u brzom slijedu; hitna medicina

Summary

Ketamine is a phencyclidine derivative (N-1-phenyl-cyclohexylpiperidine-[PCP]), an anesthetic with dissociative, analgesic and psychedelic properties, widely used in human and veterinary medicine. It has been in use since 1964. Its hallucinogenic effects led to its recreational use starting in the 1970s. Ketamine acts primarily as a non-competitive agonist of the N-methyl-D-aspartate (NMDA) receptor. With its action, it produces strong anesthesia, seadation and amnesia while maintaining spontaneous breathing. The use of ketamine nowdays is wide, except as an anesthetic it is used to treat chronic pain, and as a fast-acting antidepressant. This review article aims to provide a brief overview of the versatile uses of ketamine with an emphasis on its use in emergencies.

Key words: ketamine; anesthesia; rapid sequence intubation; emergency medicine

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Uvod

Tijekom proteklih 60 godina upotreba ketamina postala je raširena u humanoj i veterinarskoj medicini, a zbog njegovih halucinogenih svojstava 70-tih godina prošlog stoljeća započinje njegova nemedicinska upotreba kao rekreacijske droge (1). Njegov jedinstven način djelovanja, kratko trajanje i sigurnost učinili su ga važnim lijekom u hitnoj medicini i liječenju boli diljem svijeta. Proučavanje i upotreba ketamina za liječenje nekoliko novih indikacija, od bolnih sindroma do ovisnosti o drogama i psihijatrijskih poremećaja, u stalnom je porastu.

U eksperimentalnim istraživanjima, ketamin je pridonio boljem razumijevanju glutaminergičkog sustava i životinjskih modela shizofrenije (2). Iako se opioidi smatraju kamenom temeljcem u liječenju jake boli u hitnim traumatološkim stanjima, oni nedvojbeno imaju stanovite nedostatke (3). Opioidi nose i kratkoročne i dugoročne rizike, uključujući mučninu, konstipaciju, toleranciju na lijekove, respiracijsku depresiju, ovisnost, zloupotrebu i predoziranje. Prema američkim podacima, tisuće ljudi umire u Sjedinjenim Državama svake godine zbog upotrebe opioida. Godine 2021 ubilježeno je 100 000 smrtnih slučajeva predoziranja od čega 78 % zbog opioida, a opioidi na recept su činili skoro petinu trovanja (4).

Studije pokazuju da upotreba benzodijazepina i opijata u kod traumatiziranih bolesnika produžuje broj dana provedenih na strojnoj ventilaciji i ukupno trajanje boravka u bolnici (5). Jedan od većih doprinosa ketamina je njegov brzi i učinkovit antidepresivni učinak (6). Antidepresivni učinak ketamina potaknuo je daljnja istraživanja, pa ketamin, osim svoje važne uloge u anesteziji i liječenju kronične boli, ima značajan utjecaj na istraživanje i liječenje psihijatrijskih poremećaja. Edward Domino provodio je prve kliničke pokuse koji su pokazali da je ketamin siguran i kratkodjelujući anestetik. Međutim, ketamin je imao psihotropne učinke te je klasificiran kao disocijativni anestetik (7). Ketamin predstavlja smjesu dva optička stereoizomera topiva u vodi; S (+) i R (-) ketamina. Način farmakološkog djelovanja ketamina je blokada N-metil D-aspartatnih receptora (NMDAR), ionskih kanala koji su uglavnom uključeni u ekscitatornu glutamatergičku neurotransmisiju. Oba enantiomera dijele sposobnost blokiranja NMDAR-a, ali se razlikuju u svojoj snazi. S-ketamin se preferira u kliničkoj anesteziji zbog sposobnosti jačeg blokiranja NDMAR-a, dok R-ketamin ima slabiji afinitet za receptore (8).

S obzirom na brojne nove studije koje se objavljuju o ketaminu svaku godinu, pregled i ažuriranje podataka postaje izazov. Svrha ovog preglednog članka je upoznati kliničare s različitim upotrebama ketamina, od njegove uloge u liječenju određenih psihijatrijskih stanja, do terapije boli i temeljnog razumijevanja njegovih učinaka kao anestetika naročito u hitnoj medicini.

Tijekom proteklih 60 godina upotreba ketamina postala je raširena u humanoj i veterinarskoj medicini. Njegov jedinstven način djelovanja, kratko trajanje i sigurnost učinili su ga važnim lijekom u hitnoj medicini i liječenju boli.

Metode rada:

Za potrebe ovog preglednog članka pretraživana je literatura u razdoblju od 1978. do 2023., koja je bila dostupna u bazama podataka PubMed. Uključni kriteriji su bili pregledni članci, prikazi slučajeva, klinička ispitivanja, randomizirana kontrolirana ispitivanja i meta - analize o upotrebi ketamina. Isključni kriteriji su bili uvodnici, podaci dostupni jedino u sažetcima, laboratorijske studije i eksperimenti na životinjama, te radovi koji nisu na engleskom jeziku. Strategija se sastojala od pretraživanja zadanih ključnih riječi iz popisa *Medical Subject Headings* (MeSH) *Indexa Medicusa.*

Upotreba ketamina u zbrinjavanju dišnog puta

Jedna od temeljnjih vještina hitnih medicinskih postupaka pored uspostave venskog puta je zbrinjavanje dišnog puta i kontrola ventilacije. Endotrahealna intubacija (ETI) je postupak u kojem se odvaja dišni put od probavnog sustava te omogućava preuzimanje nadzora nad ventilacijom. Provodi se u slučajevima kada bolesnik ne može samostalno održavati otvoren dišni put i/ili održavati odgovarajuću ventilaciju spontanim udisajima. ETI uključuje primjenu sedativa i hipnotika za smanjenje razine svijesti, te mišićnih relaksansa radi bolje preglednosti usne šupljine, larinksa i otvorenih glasnica prilikom postavljanja tubusa. Iznimka je stanje srčanog zastoja i reanimacije, kada bolesnik ne diše spontano i svijest nije očuvana, a intubacija se može provesti bez upotrebe anestetika. Uvjeti i okruženje hitnog prijema se značajno razlikuju od uvjeta u operacijskoj sali. U hitnim stanjima najčešće se provodi intubacija u brzom slijedu (engl. *rapid sequence intubation, RSI*). Za razliku od mnogih anestetika koji se koriste za indukciju (poput tiopentala ili propofola), ketamin ne uzrokuje značajne hemodinamske poremećaje funkcije (9).

Sama ETI kao manipulacija dišnim putem je rizična i negativno utječe na hemodinamiku bolesnika. Intubacija podrazumijeva promjene u respiraciji, prelazak sa spontane ventilacije pod negativnim tlakom na kontroliranu ventilaciju pod pozitivnim tlakom. Promjene tlakova u prsnom košu mogu dovesti do smanjenja srednjeg arterijskog tlaka, što rezultira smanjenom perfuzijom ciljnih organa. Anestetici koji se koriste za indukciju mogu također doprinositi smanjenju sistemskog krvnog tlaka, što

dodatno opterećuje hemodinamske promjene, s obzirom na to da su hitni bolesnici fiziološki ranjivi i kritični. INTUBE multicentrička studija iz 2021 provedena u 29 zemalja dokazuje navedenu tvrdnju (10). Autori studije navode da je pad sistoličkog tlaka ispod 65 mmHg jednom ili sistolički arterijski tlak niži od 90 mmHg duži od 30 minuta uz potrebu za uvođenjem ili povećanjem doze vazopresora ili uvođenje bolusa tekućine većeg od 15mL/kg prisutan u 42,6 % svih hitnih intubacija. To ujedino uzimaju i kao kriterij kardiovaskularne nestabilnosti. Price i suradnici u retrospektivnoj analizi endotrahealnih intubacija tijekom hitnog zbrinjavanja pokazali su da jedino ketamin i etomidat ne dovode do značajnog smanjenja sistoličkog arterijskog tlaka u odnosu na preintubacijski period (11). U drugoj randomiziranoj kliničkoj studiji na 469 kritično bolesnih također je potvrđena hemodinamska stabilnost upotrebom ketamina i etomidata.

Osim povoljnih hemodinamskih učinaka, od svih anestetika jedino je ketaminu svojstveno očuvanje refleksa potrebnih za održavanje dišnog puta i spontanog disanja u standardnim anestetskim dozama.

Važno je istaknuti da je u toj studiji prikazana značajno veća učestalost adrenalne insuficijencije kod etomidata, što je za etomid opisana nuspojava u literaturi (12). To dodatno kvalificira ketamin kao anestetik izbora za hemodinamsku stabilnost kod RSI-a. Osim povoljnih hemodinamskih učinaka, od svih anestetika jedino je ketaminu svojstveno očuvanje refleksa potrebnih za održavanje dišnog puta i spontanog disanja u standardnim anestetskim dozama (1-3 mg/kg intravenski) (13). To mu omogućava veći vremenski razmak između sedativa i mišićnog relaksansa, što pruža značajno dodatno vrijeme za preoksigenaciju bolesnika i optimizaciju prikaza glasnica tijekom laringoskopije. Dodatno se može i povećati arterijski tlak uvođenjem vazopresora u bolusu ili samo bolusom intravenske tekućine. Ovakav način intubacije prvi puta spominje Scott Weingart 2011 i naziva ga intubacijom u odgođenom slijedu (engl. *Delayed Sequence Intubation – DSI*) (14). Dostupnost videolarigoskopije u hitnom prijemu zahvaljujući tehnološkom napretku dovela je do razvoja još jednog modaliteta endotrahealne intubacije povezane s ketaminom - intubacije čistim ketaminom uz očuvanje spontanog disanja (engl- *ketamine only breathing intubation –KOBI*) (15). Iako neki autori zagovaraju primjenu KOBI-a u bolesnika s anatomski otežanim dišnim putem, onih koji ne toleriraju niti kratkotrajnu apneu ili kod bolesnika s izraženom acidemijom (dijabetička ketoacidoza, laktacidoza), Driver i suradnici su analizom podataka američkog nacionalnog registra uspostave dišnih puteva u hitnoćama pronašli nižu učestalost uspješne intubacije, višu učestalost hipoksemije kod primjene KOBI-ja u usporedbi sa RSI-om (16).

Upotreba ketamina u proceduralnim sedacijama

Ketamin se u proceduralnoj sedaciji koristi više od četvrt stoljeća, počevši s pedijatrijskom sedacijom. (17). Proceduralna sedacija predstavlja postupak pri kojoj umjereno do duboko sediramo bolesnika u svrhu bezbolnijeg i lakšeg izvođenja određenih medicinskih zahvata, kao što su male kirurške intervencije (drenaža apscesa, zatvorena repozicija kosti), kardioloških intervencija (sinhronizirana kardioverzija, transvenski pacing) ili invazvnih pretraga (kolonoskopija, endoskopska retroholangiopankreatografija). Ketamin je jak sedacijski lijek s jedinstvenim načinom djelovanja. Za razliku od drugih anestetika, propofola, etomidata, midazolama on uzrokuje disocijaciju središnjeg živčanog sustava od izvanjskih podražaja (bol, zvuk, slika). Bolesnik je senzorički izoliran, budan s očuvanim spontanim disanjem i refleksima očuvanja dišnog puta, te održanog sistemskog tlaka, ali bez reakcije na vanjske podražaje (18). Kombinacija disocijacije, analgezije i amnezije pogodan je modalitet sedacije kod izrazito bolnih ili neugodnih procedura. Još jedna specifičnost ketamina je da potpuna disocijacija nastupa kada se prijeđe "doza praga", najčešće 1-1,5 mg/kg intravenski. Dodatna primjena ili povećanje doze ketamina ne produbljuje razinu sedacije nego samo produžava trajanje (17).

Sedacija ketaminom smatra se zasebnim kliničkim entitetom, poznatim kao disocijativna sedacija. To je kataleptičko stanje koje je nalik transu, a karakterizira ga duboka analgezija i amnezija uz očuvanje zaštitnih refleksa dišnog puta, spontanog disanja i hemodinamske stabilnosti (19). Sigurnost i učinkovitost ketamina u proceduralnoj sedaciji je potvrđena brojnim istraživanjima (20,21). U studiji Newtona i Fittona provedenoj na 92 ispitanika, zabilježeni su neželjeni događaji u 21,7 % slučajeva, od čega je 60 % bolesnika bilo agitirano pri buđenju iz sedacije. Povraćanje, hipersalivacija i kloničke kretnje su zabilježene u znatno manjim proporcijama. Od 12 bolesnika koji su pri buđenju pokazivali agitaciju, petero se spontano oporavilo u kratkom vremenskom periodu, dok je kod 7 bolesnika primjena intravenoznog midazolama dovela do prestanka agitacije (20). Tijekom proceduralne sedacije ketaminom potrebno je monitorirati bolesnika, što uključuje neinvazivno mjerenje arterijskog tlaka, EKG, perifernu saturaciju kisikom, te kapnografiju (22,23). U proceduralnoj sedaciji ketamin se primjenjuje intravenski u punoj disocijativnoj dozi od 1,5 do 2 mg/kg, što je dovoljno za 30 minuta sedacije. Iako su u prošlim desetljećima uz ketamin profilaktički primjenjivani sedativi, antiemetici i antikolinergici radi izbjegavanja neželjenih učinaka, postojeća literatura opovrgava njihovu učinkovitost, čime se dovodi u pitanje njihova opravdanost. (24).

Upotreba ketamina u obezboljavanju pri akutnoj i kroničnoj boli

Hitna medicina je prvi dio zdravstvenog sustava s kojim bolesnici dolaze u kontakt u akutnim, a često i kroničnim

bolnim stanjima. Za analgeziju bolesnika ketaminom koriste se značajno niže doze 0,1 - 0,3 mg/kg intravenski, koje ne uzrokuju disocijaciju i djeluju isključivo analgetski. Više od dva desetljeća anesteziologija istražuje primjenu niskih analgetskih doza ketamina, koju hitna medicina preuzima i usvaja (25). Godine 2005. Elia i Tramer objavili su sustavni pregled radova o analgetskim učincima ketamina pri liječenju poslijeoperacijske boli (26). I druge studije s početka 2010-tih evaluiraju analgetske učinke ketamina u suzbijanju akutne boli u bolesnika na hitnom prijemu (27). Brojne studije pokazuju da su niske doze ketamina ekvivalentne opioidima po analgetskom učinku, bilo u bolusu, kratkotrajnoj ili kontinuiranoj infuziji. Razlike u neželjenim učincima između ketamina i opioida nisu statistički značajne (28). Osim intravenske primjene najnovije studije istražuju primjenu nebuliziranog i intranazalnog ketamina (29,30).

Sedacija ketaminom smatra se zasebnim kliničkim entitetom poznatim kao disocijativna sedacija, kataleptično stanje nalik transu, a karakterizira ga duboka analgezija i amnezija uz očuvanje zaštitnih refleksa dišnog puta, spontanog disanja i hemodinamske stabilnosti.

Upotreba ketamina pri sedaciji akutno agitiranog bolesnika

Ketamin se pokazao učinkovitim sredstvom u liječenju akutno agitiranih bolesnika u hitnom prijemu. 2010.-tih godina, uz proučavanje analgetskih učinaka ketamina, provedena su istraživanja o njegovoj primjeni u akutno agitiranim stanjima. Postoji nekoliko standardnih protokola primjene ketamina, pri čemu se najčešće primjenjuju doze od 5 mg/kg intramuskularno. Intramuskularna primjena ketamina osobito je pogodna u izvanbolničkim uvjetima (32). Zahvaljujući brzom nastupu sedacije u svega nekoliko minuta, 4,2 minute u studiji Colea i suradnika (32) ketamin se pokazao učinkovitijim od primjene benzodijazepina i haloperidola u kombinaciji, koji počinju djelovati prosječno za 15 minuta. Upotreba ketamina pri sedaciji akutno agitiranih bolesnika dobro je istražena i postoje studije koje govore tome u prilog (33,34).

Neželejni učinci i kontraindikacije ketamina u hitnoj službi

Ketamin je siguran lijek s malim brojem neželjenih učinaka i kontraindikacija. Ima negativne inotropne učinke, ali u dozama višestruko većim od standardnih (20 mg/kg dok je anestetska doza 1-3 mg/kg). Iako postoje malobrojne studije s niskim brojem uključenih bolesnika koje navedeno potvrđuju i u standardnim anestetskim dozama (35), suprotstavljaju im se brojnije studije koje potvrđuju njegovo pozitivno djelovanje na hemodinamiku (36). Kao strukturni analog fenciklidina, može izazvati određene psihomimetičke neželjene učinke, kao što su halucinacije, noćne more, disforičnost, čak i privremeni poremećaj vida (37). Cistitis isto kao i hepatotoksičnost ketamina neželjeni su učinci ketamina primarno zabilježena kod kronične zloupotrebe u rekreacijske svrhe (38). Ketamin može uzrokovati mučninu i povraćanje, a retrospektivne studije navode incidenciju od 2,8 do 6,5 % (39). Apsolutna kontraindikacija je preosjetlljivost na ketamin, ostale su kontraindikacije relativne počevši od povišenog intrakranijskog tlaka, angine pektoris, neregulirane arterijske hipertenzije i psihijatrijskih poremećaja. Brojne studije su dokazala da povećanje intrakranijskog tlaka zanemarivo s obzirom na održani perfuzijski tlak u mozgu i nepromijenjene neurološke ishode (40,41), a neke studije su pokazale da do povećanja kako intrakranijskog, tako i intraokularnog tlaka ne dolazi (41). Angina pektoris i neregulirana arterijska hipertenzija svrstane su u relativne kontraindikacije zbog simpatomimetičkog djelovanja ketamina i mogućeg pogoršanja osnovne bolesti zbog povećane aktivnosti simpatikusa. Bolesnici koji boluju od shizofrenije mogu nakon primjene ketamina razviti halucinacije i sumanute misli, stoga se preporučuje oprez pri njegovoj primjeni u ovoj skupini bolesnika (42). Ostale relativne kontraindikacije su dekompenzirana ciroze jetre, feokromocitom, trudnoća i hipertireoza (mogućnost pogoršanja uslijed aktivacije simpatikusa).

Zaključak

Ketamin je nezaobilazan lijek u primjeni u hitnim stanjima. Koristi se kao analgetik, sedativ i anestetik zbog svojih jedinstvenih karakteristika. Ketamin je čest izbor u bolesnika s hemodinamskom nestabilnošću, jer održava sistemski krvni tlak i srčani minutni volumen, za razliku od drugih lijekova. Djeluje brzo i pruža dobru analgeziju, posebno kod trauma i bolnih postupaka, dok istovremeno omogućava sedaciju. Ketamin ne uzrokuje respiracijsku depresiju, što ga čini sigurnim u slučajevima prijetećeg zatajenja disanja. Psihomimetički učinci ketamina, poput halucinacija i disforije, neželjeni su učinci koji se uspješno kontroliraju primjenom benzodijazepina. Koristi se često i uspješno za proceduralne sedacije kod djece i odraslih zbog dobre tolerancije i sigurnosnog profila. Ketamin igra ključnu ulogu u zbrinjavanju dišnog puta u hitnim stanjima, posebno pri intubacijama u brzom slijedu. Iako je široko primjenjiv u hitnoj medicini, zahtijeva pažljivo praćenje zbog svojih psiholoških učinaka i mogućnosti izazivanja hipertenzije.

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ORIGINAL ARTICLE / IZVORNI ZNANSTVENI ČLANAK

HYPERGLYCAEMIA IN CRITICAL ILLNESS IN NON-DIABETICS IS ASSOCIATED WITH INCREASED INTRINSIC INSULIN RESISTANCE

HIPERGLIKEMIJA U KRITIČNO OBOLJELIH BOLESNIKA BEZ DIJAGNOZE ŠEĆERNE BOLESTI POVEZANA JE S POVEĆANOM INZULINSKOM REZISTENCIJOM

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Abstract

Introduction: Hyperglycemia commonly occurs in the course of critical illness, both in patients with and without apparent glucose metabolism disorder. Insulin resistance is characterized by the reduced response of tissues to insulin. We hypothesized that one of the causes of hyperglycemia in critical illness among patients without apparent glucose metabolism disorder is intrinsically increased insulin resistance.

Patients and methods: Patients with no history of impaired glucose metabolism admitted to a medical intensive care unit due to critical illness were included. They were divided into hyperglycaemia group (glucose >7.7 mmol/L, on at least two occasions) and normoglycaemia group. Glycated hemoglobin during hospital stay and oral glucose tolerance test within 6-8 weeks after discharge were performed, patients with unknown diabetes or pre-diabetes were excluded. On the follow up visit 6-8 weeks after discharge insulin resistance was assessed by indirect methods using simple indices: QUICKI, HOMA-IR, log HOMA-IR and HOMA2-IR.

Results: Research was concluded on 221 patients: 114 in hyperglycaemia group and 107 in normoglycaemia group. There were no significant differences in age nor sex among groups. BMI, WHR and positive family history of type 2 diabetes had higher values in hyperglycaemia group. Patients in hyperglycaemia group had higher insulin levels (75.5 pmol/l vs 62.8 pmol/l, $p<0.001$) and higher insulin resistance assessed by simple insulin resistance indices compared with patients in normoglycaemia group. Multivariate logistic regression analysis showed independent association of BMI, WHR, HOMA-IR and QUICKI with occurrence of hyperglycemia in acute illness.

Conclusion: Occurrence of hyperglycemia in critical illness among patients without apparent glucose metabolism disorder is associated with intrinsically increased insulin resistance.

Key words: hyperglycaemia in critical illness; insulin resistance; prediabetes

Sažetak

Uvod: Hiperglikemija je česta pojava tijekom teške akutne bolesti i u bolesnika sa šećernom bolesti, ali i u bolesnika bez očitog poremećaja metabolizma glukoze. Inzulinska rezistencija karakterizirana je smanjenim odgovorom tkiva na inzulin. Naša hipoteza bila je da je intrinzička inzulinska rezistencija jedan od čimbenika koji dovodi to evidentnog poremećaja glikemije u teškoj akutnoj bolesti.

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Bolesnici uključeni u studiju nisu imali anamnezu poremećaja metabolizma glukoze i primljeni su u internističku jedinicu intenzivne medicine zbog teške akutne bolesti. Podijeljeni su u dvije skupine: hiperglikemijsku skupinu (glukoza >7,7 mmol/L u najmanje dva navrata) i normoglikemijsku skupinu. Glikirani hemoglobin (A1c) tijekom hospitalizacije, te oralni test tolerancije glukoze provedeni 6-8 tjedana nakon otpusta korišteni su za isključivanje bolesnika sa šećernom bolešću koja nije bila prepoznata prije hospitalizacije. Na kontrolnom pregledu 6-8 tjedana po otpustu određena je inzulinska rezistencija pomoću indirektnih metoda: QUICKI, HOMA-IR, log HOMA-IR i HOMA2-IR.

Rezultati: Istraživanje je uključilo 221 bolesnika: 114 u skupini hiperglikemije, 107 normoglikemičnih. Nije bilo statistički značajne razlike u spolnoj raspodjeli i dobi između skupina; hiperglikemijska skupina imala je viši indeks tjelesne mase, viši omjer struka i bokova te češće pozitivnu obiteljsku anamnezu za tip 2 šećerne bolesti. Bolesnici u hiperglikemijskoj skupini imali su više razine inzulina (75.5 pmol/l) u usporedbi s normoglikemijskom skupinom (62,8 pmol/l; p<0.001) te više razine inzulinske rezistencije mjerene bilo kojom metodom. Multivarijatna analiza logističkom regresijom pokazala je neovisnu povezanost indeksa tjelesne mase, omjera struka i bokova, HOMA-IR i QUICKI s pojavom hiperklikemije akutne bolesti.

Zaključak: Pojava hiperglikemije akutne bolesti u bolesnika bez evidentnog poremećaja metabolizma glukoze povezana je s povišenom intrinzičkom inzulinskom rezistencijom.

Ključne riječi: hiperglikemija u akutnoj bolesti; predijabetes; inzulinska rezistencija

Introduction

Hyperglycaemia commonly occurs during the course of any critical illness: regularly among patients with diabetes or pre-diabetes, but also in patients without apparent glucose metabolism disorder. It is associated with worse clinical outcomes including morbidity, mortality and length of hospital stay, infection and overall complication rates (1-7). Also, non-diabetics who developed hyperglycaemia in critical illness should be considered as a population at increased risk for developing diabetes (8-14).

Insulin resistance is characterized by reduced response of tissues to insulin. It is a crucial part of metabolic syndrome, a key factor in development of type 2 diabetes, closely linked to obesity and is an underlying cause of cardiovascular and neurodegenerative diseases (15-17). Its inheritance is somewhat elucidated by genome wide association studies (GWAS) (18).

Despite the fact that stress and inflammatory response occur among all critically ill patients, evident hyperglycaemia is not encountered in all of them. We hypothesized that the predisposition for hyperglycaemia in critical illness among patients without apparent glucose metabolism disorder lies in previously developed insulin resistance of those patients.

Patients and methods

This was a prospective observational study performed in the medical intensive care unit (ICU) of the University Hospital Centre Zagreb.

Adult patients with negative history of diabetes mellitus (DM), impaired fasting glucose (IFG) or impaired glucose tolerance (IGT) admitted to the ICU due to critical illness were included. The term critical illness in this study covered a spectrum of diseases, the most common being acute coronary syndrome, sepsis and septic shock, pneumonia and lung oedema, which represent most common admission diagnosis in our ICU. Negative history of existing glucose metabolism disorders was confirmed with HbA1c measurement and oral glucose tolerance test (OGTT) performed 6-8 weeks after hospitalization.

Patients who were diagnosed with glucose metabolism disorder (DM, IFG, IGT) during hospitalization or at the follow-up visit were excluded from the study. Patients with glucocorticoid treatment during or 8 weeks before admission, those with known endocrine disorder that might alter glucose metabolism, and those with end-stage disease were also excluded from the study. We did not include patients who were unwilling to participate and those with acute or chronic condition that might cause early fatality or hinder follow up.

The following data were collected for all patients: age, sex, body mass index (BMI), family history of diabetes, history of smoking, serum cholesterol and triglycerides concentrations. Admission Acute Physiology and Chronic Health Evaluation (APACHE II) and waist to hip ratio (WHR) were calculated for all patients (19,20), Sequential Organ Assessment Score (SOFA) was scored daily and the

highest score was used as a measure of disease severity (21,22). Plasma glucose (venous) was measured at least twice daily (6 A.M. and 6 P.M.). Additional measurements were performed in patients whose blood glucose was variable or in cases where insulin was administrated to treat hyperglycaemia. Plasma glucose concentration was analyzed with enzymatic method-photometry UV with hexokinase on Cobas c501/c311, Roche device or using point-of-care analyzer (IL GEM Premier 3000 Electrolyte Analyzer, Instrumentation Laboratories, Lexington, MA, USA).

Patients were fed according to the Department policy with target caloric intake set on 15 kcal/kg/day. Enteral nutrition was started not later than 24 hours after admission, in cases where enteral nutrition was not tolerated or contraindicated, parenteral nutrition was performed.

According to the measured glucose levels patients were divided in two groups: hyperglycaemia group and normoglycaemia group. The hyperglycaemia group was comprised of patients whose glucose level was at least in two occasions higher than 7.7 mmol/L (140 mg/dL). All other patients formed the normoglycaemia group.

Patients included in the study had a follow-up visit performed 6-8 weeks after hospital discharge, during which fasting blood samples were collected and OGTT was performed according to WHO recommendation (23). Fasting blood samples of patients with normal OGTT values were centrifuged and the serum was stored in refrigerator settings of -20 °C. Serum insulin concentration was gained through electrochemiluminescence method on Cobas E 601, Roche device, with Roche Elecsys/E170 test (Roche Diagnostics, Indianapolis, Indiana). Insulin resistance was expressed with simple insulin resistance indices: QUICKI (24), HOMA-IR (25,26), log HOMA-IR, HOMA 2-IR, HOMA 2-%S. HOMA 2-IR, HOMA 2-%S and beta cell function (HOMA 2%-B) were derived through the same HOMA2 computer model (27).

Definitions

Impaired fasting glucose (IFG), impaired glucose tolerance (IGT) and diabetes mellitus (DM) were defined according to the ADA criteria (28). Sepsis, severe sepsis and septic shock were defined according to the usual criteria (29,30). Acute coronary syndromes were defined according to the ACC/AHA criteria (31-33).

Statistical analyses

MedCalc 22.017 and SPSS 17.0 were used for all statistical analyses. Categorical data are presented as absolute and relative frequencies, continuous variables as median with standard deviation. Chi square test was used for categorical variable while Student's t-test was used for continuous variables. Multivariate logistic regression analysis was performed using logistic regression. Statistical significance was set at $\alpha = 0.05$.

The study was approved by the Ethics Committee of the University Hospital Centre Zagreb. All patients included in the study signed an informed consent form. The study was not funded or supported by any organization, group or individual.

Table 1. Characteristics of patients included in the study

	All patients (N=221)	Patients with hyperglycaemia (N=114)	Patients without hyperglycaemia (N=107)	p
Age (years)	51±14	51±15	50±13	0.605
Female sex (N, %)	87 (39%)	41 (36%)	46 (43%)	0.784
Body mass index (kg/m^2)	27±4	28.4±4.6	26.4±3.4	0.002
Waist to hip ratio	1.05±0.13	1.07±0.11	0.99±0.11	<0.001
Total cholesterol (mmol/L)	4.6±0.97	4.7±1.0	4.5±0.9	0.300
Triglycerides (μmol/L)	3.2±1.1	3.1±1.1	3.2±1.0	0.165
Highest glucose level in acute illness (mmol/L)	8.1±3.7	9.3±4.1	6.9±3.2	0.005
APACHE II score	18.4±3.9	19.5±4.9	17.3±3.7	0.001
SOFA score	3.1±0.6	3.2±0.6	2.8±0.5	0.003
Family history of DM (%)	54 (24.4 %)	34 (32.7 %)	20 (18.7 %)	0.029
Smoking	50 (22.6 %)	28 (26.9 %)	32 (27.3 %)	0.936

APACHE: Admission Acute Physiology and Chronic Health Evaluation; SOFA: Sequential Organ Assessment; DM: diabetes mellitus

Hyperglycemia is prevalent in critical illness, particularly among patients with diabetes or prediabetes, but it can also occur in those without any obvious glucose metabolism disorders.

Results

The study included a total of 221 patients: 114 in hyperglycaemia group and 107 in normoglycaemia group. There were no statistically significant differences in age or sex between the two groups. Body mass index, waist-to-hip ratio and positive family history of DM were significantly higher among patients in hyperglycaemia group (Table 1).

APACHE II and SOFA scores were higher in the hyperglycemia group, but multivariate logistic regression analysis did not point those scores as independent predictors of hyperglycaemia occurrence. Patients who developed hyperglycaemia during critical illness had higher insulin resistance according to all simple indices of insulin resistance: QUICKI, HOMA-IR, log HOMA-IR, HOMA 2-IR, as shown in Table 2.

On the follow-up visit patients from hyperglycaemia group had higher fasting glucose level (4.7 mmol/l vs. 4.6 mmol/L), but that difference did not show as statistically significant (p=0.414). Fasting insulin level was higher in the hyperglycaemia group (75.5 pmol/l vs 62.8 pmol/l), p<0.001. Function of beta cell did differ among the groups with higher values in hyperglycaemia group (141.9 vs 130.7), but the difference was not statistically significant (p<0.07).

Multivariate analysis with logistic regression (Table 3) pointed out independent correlation between body mass index and waist-to-hip ratio with occurrence of hyperglycaemia in critical illness. It also showed independent correlation of both HOMA-IR and QUICKI with hyperglyceamia in critical illness.

Table 2. Insulin resistance of patients included in the study

	Patients with hyperglycaemia (N=114)	Patients without hyperglycaemia (N=107)	p
Glucose level (mmol/L)	4.7 ± 0.5	4.6 ± 0.56	0.414
Insulin (pmol/L)	75.5 ± 16.1	62.8 ± 11.0	<0.001
QUICKI	0.339 ± 0.009	0.349 ± 0.006	<0.001
HOMA-IR	2.245 ± 0.417	1.839 ± 0.224	<0.001
Log HOMA-IR	-0.244 ± 0.079	-0.268 ± 0.053	<0.001
HOMA 2-IR	1.37 ± 0.27	1.14 ± 0.17	<0.001
HOMA 2-%B	141.9 ± 47.9	130.7 ± 43.5	0.070
HOMA 2-%S	75.7 ± 15.2	89.5 ± 13.4	<0.001

Disscusion

The group of patients who developed hyperglycaemia in critical illness has statistically higher level of insulin resistance after hospitalization according to all simple indices in comparison with the group of patients which remained normoglycaemic during critical illness.

Since the definition of hospital acquired hyperglycaemia was not universal at the moment we started the study threshold was set on 7.7 mmol/L (140 mg/dL). This cut-off value was taken from previous studies dealing with occurrence of hyperglycaemia in critical illness among non-diabetics (10).

Study design with strict inclusion/exclusion criteria and 6-8 weeks delay until insulin resistance measurements aimed to assure insulin resistance was not elevated due to acute illness or pre-existing diabetes

Feeding regimen and caloric intake could have played a role in development of hyperglycaemia, but it did not differ between the groups in caloric intake nor in feeding strategy.

Patients who developed hyperglycaemia during critical illness showed higher insulin resistance after hospitalization, suggesting that intrinsic insulin resistance is a key contributor to hyperglycaemia. This highlights the role of metabolic factors in the development of hyperglycaemia in critically ill patient

Positive family history of diabetes was more often in hyperglycaemia group. Due the importance of family history in diabetes (34) and insulin resistance being known part of the disease progression (15), it was not surprising to find patients genetically predisposed to diabetes in the group with intrinsically increased insulin resistance which developed hyperglycaemia during the critical illness.

Higher BMI and waist-to-hip ratio were seen among the hyperglycaemia group patients. These results were expected due to diabetes- obesity relationship (35,36).

Hyperinsulinemic euglycemic clamp (HEC) is the gold standard for the measurement of insulin sensitivity, but surrogate indices used in this study (QUICKI, HOMA-IR) seem to be appropriate to assess insulin resistance (37-39).

Relatively small number of medical ICU patients involved in the study represents its strongest limitation. Even though we expect same results among patients without glucose metabolism disorder hospitalized in surgical ICU who developed hyperglycaemia in critical illness, in the future research should be broaden to those patients as well.

We suggest that increased levels of the intrinsic insulin resistance are a major contributor of hyperglycaemia in

Table 3. Independent predictors of hyperglycaemia occcurrence in multivariate logistic regression analysis

Variable	OR (95% CI)	P
BMI, for each increase of 1.0 kg/m^2	1.23 (1.11 – 1.36)	0.001
WHR, for each increase of 0.1	2.56 (1.79 – 3.64)	<0.001
HOMA-IR, for each increase of 0.1	6.58 (1.59 – 27.34)	0.036
QUICKI, for each change of 0.01	25.1 (1.25 – 49.8)	0.041

BMI: body mass indeks; WHR: waist to hip ratio

critical illness. Like survivors from ICU who had transitory hyperglycaemia, women with a history of gestational diabetes (GDM) are in risk for future type 2 diabetes (40). These women are shown to be more insulin resistant (41,42).

Higher body mass indeks, waist-to-hip ratio, and a family history of diabetes were more common in the hyperglycaemia group, indicating a predisposition to insulin resistance and diabetes.

We hypothesize that metabolic disorder which makes some individuals prone to hyperglycaemia in critical illness (10) involves increases already relatively high insulin resistance what makes compensation by enhanced beta cell function more difficult, especially if beta cells have some degree of disfunction (15). We may conclude that hyperglycemia in critical illness reveals increased insulin resistance and predisposition for later development of diabetes.

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REVIEW ARTICLE / PREGLEDNI ČLANAK

UPDATING THE 5 ES OF EMERGENCY PHYSICIAN PERFORMED CARDIAC POINT-OF-CARE ULTRASOUND: A PROTOCOL FOR RAPID IDENTIFICATION OF EFFUSION, EJECTION, EQUALITY, EXIT, AND ENTRANCE

DOPUNA 5 "E" NALAZA ULTRAZVUKA SRCA IZVOĐENOG OD STRANE LIJEČNIKA HITNE MEDICINE UZ KREVET BOLESNIKA: PROTOKOL ZA BRZU PROCJENU IZLJEVA, EJEKCIJSKA FRAKCIJE, SIMETRIJE, IZLAZNIH I ULAZNIH PROTOKA

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Abstract

The 5 Es (effusion, ejection, equality, exit, and entrance) are a protocol developed in 2015 to standardize the performance and interpretation of cardiac point-of-care ultrasound (POCUS). Since its publication, cardiac POCUS has advanced, including the advent of artificial intelligence and additional research that refines and reinforces the 5 Es in cardiac POCUS. This review discusses these advances. The 5 Es continue to serve as a protocol to guide both novice and advanced ultrasonographers in identifying emergent pathology.

Key words: cardiac point-of-care ultrasound; echocardiogram; aorta; pericardial effusion; myocardial infarction

Sažetak

Protokol 5 E (efuzija, ejekcija, jednakost, izlaz i ulaz) je razvijen 2015. godine kako bi se standardizirala izvedba i interpretacija kardiološkog ultrazvuka uz krevet boolesnika (engl. *point-of-care ulttrasound, POCUS*). Od njegove objave, kardiološki POCUS značajno je napredovao, uključujući primjenu umjetne inteligencije i nova istraživanja koja dodatno usavršavaju i potvrđuju važnost 5 E u kardiološkoj ultrazvučnoj dijagnostici. Ovaj pregled razmatra te napretke. Protokol 5 E i dalje služi kao protokol za prepoznavanje hitne patologije, kako početnicima tako i iskusnim liječnicim.

Ključne riječi: ultrazvuk uz krevet bolesnika u kardioloških bolesnika; ultrazvuk srca; aorta; efuzija perikarda; infarkt srca

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Introduction

Cardiac point-of-care ultrasound (POCUS) has been performed in the Emergency Department (ED) for over 30 years and is among the most performed POCUS examination type both on its own and in combination with symptom-based protocols (1,2). A protocol described as the "5 Es" was proposed by our group in 2015 to help emergency physicians (EPs) assess for cardiac pathologies using POCUS (3). POCUS has continued to expand in both undergraduate medical education and residency training (3-6). The 5 Es are effusion, ejection, equality, exit, and entrance, and offer a way to standardize the performance and interpretation of cardiac POCUS.

While the 5 Es protocol offers a straightforward approach to cardiac POCUS, there has been additional evidence on the utility of cardiac POCUS published in the 10 years since the 5 Es protocol was first proposed. Advances in POCUS equipment, increased sonographer skills, and further research have helped to solidify the use of cardiac POCUS to make more accurate diagnoses of more conditions in the ED. Additionally, there is an increasing focus on artificial intelligence (AI) in cardiac POCUS, and these new tools help sonographers make accurate diagnoses with limited training (7-10).

This review aims to update the 5 Es and discuss further supporting research including any reinforcements or changes within the past 10 years, so that this approach can continue to serve as a tool for education and practice. Reading the original 5 Es manuscript prior to this review is recommended (3).

Effusion

Assessing for a pericardial effusion involves the operator using all cardiac views to look for a fluid collection in the pericardial space. A pericardial effusion can be graded from small (< 1 cm; 50-100 mL), moderate (1-2 cm; 100-500 mL), or large (> 2 cm; >500mL) (11). If a pericardial effusion is identified, the operator should evaluate for evidence of cardiac tamponade using the inferior vena cava (IVC) diameter and lack of collapsibility, mitral or tricuspid valve inflow velocity variation, visualization of right atrial (RA) systolic and/or right ventricle (RV) diastolic collapse, or hepatic venous flow patterns (11,12). Timely and accurate detection of a pericardial effusion is essential for expediting diagnosis and management, with POCUS having been shown to decrease the time to intervention (drainage) for patients with pericardial effusions (13). A recent study showed, however, that there is poor interrater reliability for some signs of cardiac tamponade. The lowest interrater reliability was found in parasternal short views and the highest in mitral valve inflow variation, suggesting that multiple images and clinical context should be used to diagnose cardiac tamponade (14). It is important to consider that conditions such as pulmonary hypertension may affect the pathophysiology of cardiac tamponade. A recent systematic review of 43 studies showed right-sided chamber collapse appears to be less likely to occur in the setting of increased intracardiac pressure and RV hypertrophy due to pulmonary hypertension (15). Among the results, it was found that the incidence of tamponade increased in patients with pulmonary hypertension. Additionally, only 10.5 % of patients with pulmonary hypertension and tamponade showed right-sided chamber collapse, suggesting that the elevated right heart pressures withstood a higher pericardial pressure prior to collapse (15). Evaluation for the presence of pulmonary hypertension can be performed by looking for tricuspid regurgitation (TR) and measuring the pressure gradient using continuous wave Doppler, as discussed in the section on "E" for equality.

Artificial intelligence (AI) and the use of deep learning algorithms could help identify pericardial effusions, and eventually, signs of cardiac tamponade. While to our knowledge there are no commercially available products that detect pericardial effusion or signs of cardiac tamponade, there are publications showing the feasibility of detecting and quantifying pericardial effusion. Cheng et al. developed a machine-learning algorithm to automatically calculate the width of a pericardial effusion using ultrasound video clips (16). Additionally, a deep learning algorithm has been used to calculate mitral valve inflow velocities (17). As of this writing there is a preprint of a manuscript that reports reasonable accuracy in detecting moderate to large effusions and signs of tamponade (18). These novel AI applications demonstrate a proof of concept that in the future the diagnosis of cardiac tamponade could be automated.

Ejection

Assessing for overall left ventricular (LV) cardiac function or "ejection" can help provide immediate information in patients with chest pain, shortness of breath, hypotension, or syncope. Prior research has shown that emergency physicians are accurate in visually determining whether ejection fraction (EF) is preserved (EF > 50%), moderately reduced (EF 30-50%), or poor (EF < 30%) without needing to assess the EF quantitatively (19-21). POCUS operators can use this information to make a new diagnosis of congestive heart failure, expediting patient workup and care.

The last decade has seen significant improvements in POCUS technology, sonographer skills, and research, enhancing its ability to diagnose various cardiac conditions. Artificial intelligence (AI) is now playing a crucial role, helping less experienced users make accurate diagnoses.

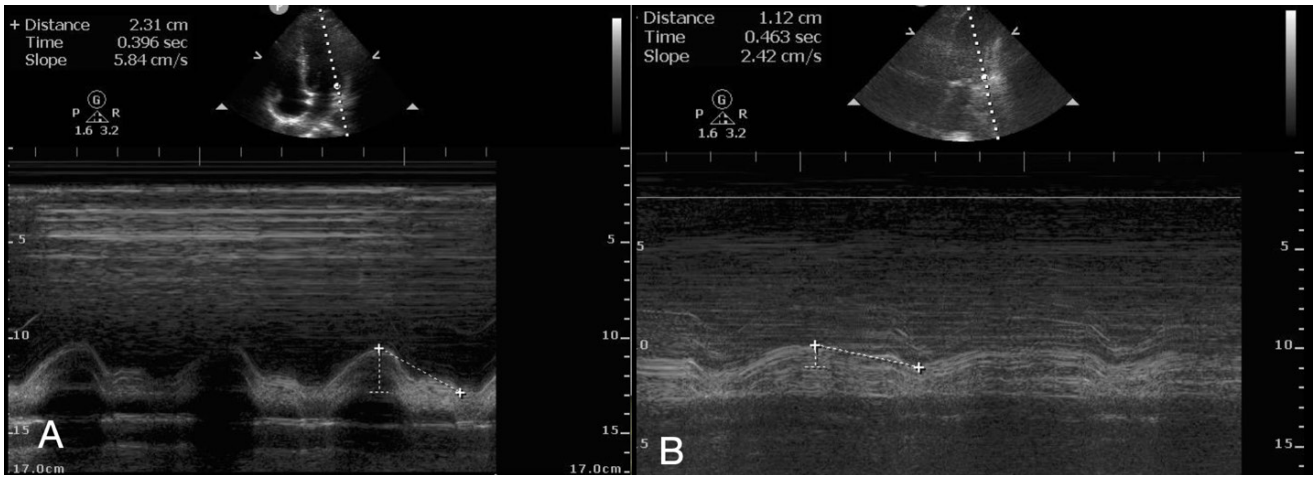

Figure 1. Normal (A) and Abnormal (B) Mitral Annular Plane Systolic Excursion in the Apical 4-Chamber View

Mitral annular plane systolic excursion (MAPSE) has recently emerged as an adjunct to help assess LV function (22,23). MAPSE is performed by performing an M-mode evaluation of the lateral annulus of the mitral valve and measuring peak to trough of the resulting wave (Figure 1). A MAPSE < 8 mm predicts an ejection fraction < 50 %, whereas normal is between 12-15 mm. MAPSE can be beneficial when the E-point septal separation (EPSS) is inaccurate such as in mitral stenosis or LV hypertrophy and the operator desires confirmation beyond visual estimation of an abnormal LV function (24).

In addition to the visual estimation of qualitative LV ejection, ultrasound manufacturers have developed proprietary software which automatically calculates an ejection fraction using Simpson's biplane method, similar to what cardiologists use in comprehensive echocardiograms (10,25). These applications can be found in both cart-based machines and handheld machines, and have been found in studies to be accurate in comparison to visual estimation by sonographers (26-28). These AI applications require an adequate apical four-chamber or apical two-chamber view to allow the software to identify and outline the LV wall in systole and diastole. The apical two-chamber view is obtained by first obtaining the apical four-chamber view and then rotating the indicator counterclockwise so that the RV is out of sight and the inferior and anterior walls of the LV are seen along with the left atrium (Figure 2). Operators using these tools can now more precisely quantify an EF, which can help both guide the admitting team and better assess changes from prior echocardiograms.

While ejection is meant to describe the overall global cardiac function, as skills with cardiac POCUS advance, operators can incorporate evaluation for focal wall motion abnormalities (FWMA). Assessing all walls circumferentially in the parasternal short axis (PSSA) using SALPI (septal, anterior, lateral, posterior, inferior walls) ensures that all myocardial walls are evaluated (Figure 3). In the setting of an occlusive myocardial infarction, even without ST segment elevation, a FWMA can suggest the need for cardiac catheterization early in the patient course, even before troponin results (29,30). The apical four-chamber and apical two-chamber views can also be used to assess for FWMA, and improve detection of apical FWMA (31). AI programs have also been shown to be accurate in detecting FWMA after training (32). Speckle tracking to look for myocardial strain has also been shown to be effective in identifying myocardial damage prior to ST elevations on the electrocardiogram, and the technology has been added to POCUS machines (33-35). There are limitations of speckle tracking including the need for software upgrades to ultrasound machines, the use of cardiac leads to ensure accurate identification of systole and diastole, and that it may not be sensitive enough to detect acute coronary syndrome accurately (34).

POCUS remains highly effective in detecting pericardial effusions and assessing for cardiac tamponade. Recent studies emphasize the importance of multiple images and clinical context for accurate diagnosis, particularly in challenging cases like pulmonary hypertension.

The assessment for FWMA can be improved either by placing a finger directly in the center of the screen to assess whether all walls equally collapse, or by blocking off other walls with a hand to limit the assessment to one wall at a time. A pitfall in assessing for FWMA in the PSSA only is that the assessment is limited to the mid-papillary view of the LV. Additionally, if the view is oblique, meaning the LV is elliptical instead of round, it can mimic a FWMA and lead to an incorrect interpretation. Finally, the presence of

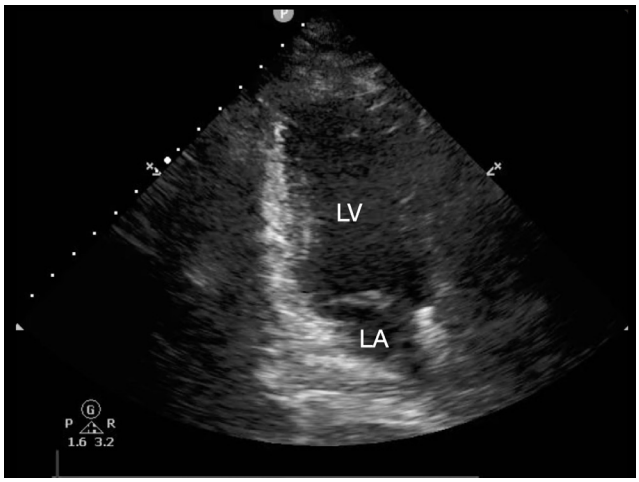

Figure 2. Apical 2-Chamber View with the Left Ventricle (LV) and Left Atrium (LA) Visualized. In this view the inferior wall is seen to the left of the image, while the anterior wall is to the right. This image is obtained by rotating the probe counterclockwise from the apical 4-chamber view. This image shows an emergency medicine orientation (indicator to screen left), so the indicator should be directed inferiorly. Should a cardiology orientation be used (indicator to screen right) the indicator should be directed superiorly after rotation.

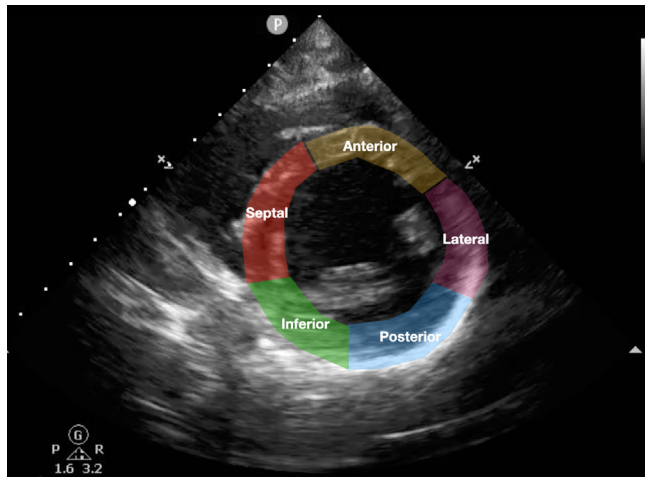

Figure 3. Parasternal Short Axis View with Left Ventricular Wall Names (SALPI)

a FWMA does not indicate when the myocardial damage occurred, and patients with a past medical history of a myocardial infarction may have residual FWMA on POCUS. The finding of a FWMA should be contextualized with the patient's electrocardiogram and presenting symptoms.

Ejection also includes the lack of myocardial activity in cardiac arrest. The use of POCUS in cardiac arrest has expanded in recent years, and getting a limited cardiac view within the 10 second pulse check is important to assess for a cause of cardiac arrest (36-38). There is, however, a significant discrepancy among ultrasound trained emergency physicians as to what defines cardiac standstill in both the adult and pediatric populations, and there has yet to be a consensus on the topic (39,40). Cardiac function is a continuum, and where to separate what constitutes significant or meaningful cardiac activity from agonal myocardial twitches can be difficult. In our experience, the lack of full valvular closure of the mitral or tricuspid valves typically indicates the lack of significant myocardial activity.

The lack of significant myocardial activity on POCUS is associated with poor patient outcomes and should be considered in the decision to cease resuscitation (41). The optimal view for visualizing cardiac activity in cardiac arrest has also come into question, as the subxiphoid view can be difficult to get in patients with a larger body habitus or with abdominal distension (38). An apical four-chamber view can visualize the heart without interfering with the compressions, and can be easier to obtain than the subxiphoid view. In the event other views are unable to be obtained, a parasternal long axis (PSLA) view can be utilized. However, care must be taken to remove any ultrasound gel from the anterior chest wall prior to compressions resuming. A recent study by Rolston et al. has shown no difference in success rate between the subxiphoid, apical four-chamber, or PSLA views when reviewing video of resuscitations (42).

POCUS can quickly evaluate left ventricular function, offering critical insights into conditions like heart failure. New tools, such as mitral annular plane systolic excursion and AI-driven ejection fraction measurements, help refine diagnosis.

POCUS can also be used during cardiac arrest to guide the appropriate location of compressions. In particular, when using a device such as the Lund University Cardiopulmonary Assist System (LUCAS) cardiac POCUS can help guide appropriate device placement. Appropriate compressions should adequately compress the left ventricular rather than the inferior vena cava or aortic outflow tract (43,44).

Equality

Equality refers to the relative size of the RV to the LV. The ratio of the RV:LV is classically less than 0.6:1, with the ratio increasing as the RV dilates secondary to an increase in pulmonary arterial pressure (3). We have suggested using "equality," or a 1:1 RV:LV ratio as the cutoff when assessing for RV dilation. Although this finding is specific, it has lower sensitivity (45,46). RV dilatation can be acute, chronic, or acute-on-chronic, and may be secondary to a

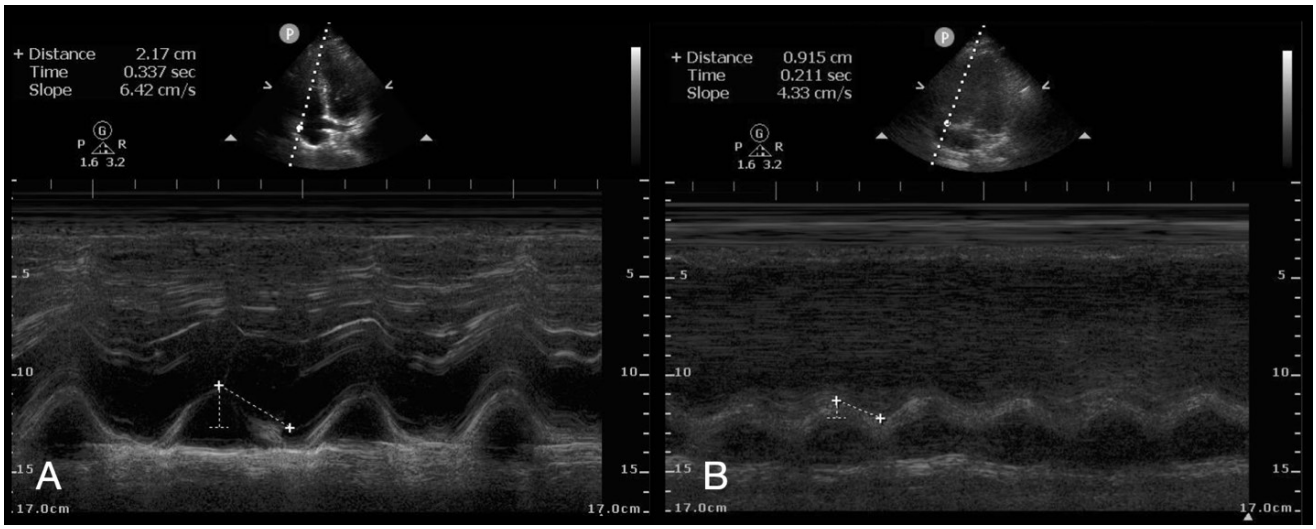

Figure 4. Normal (A) and Abnormal (B) Tricuspid Annular Plane Systolic Excursion in the Apical 4-Chamber View

multitude of pathologies besides pulmonary embolism (PE) such as long-standing pulmonary arterial hypertension, acute chest syndrome, cardiac arrest, RV ST-elevation myocardial infarction, or cor pulmonale (46).

The implementation of Pulmonary Embolism Response Teams (PERT) has emerged in the last decade with aims to improve, expedite, and standardize PE treatment, particularly in higher risk PE (47). The presence of right heart strain in a suspected or documented PE can be rapidly determined by the team at the bedside using cardiac POCUS. The presence of RV strain (with or without biomarkers) places the patient into an intermediate or higher risk zone which may be more appropriately treated with catheter directed therapies or systemic thrombolysis (48).

While the use of an RV:LV ratio cutoff of 1:1 or greater is more specific than sensitive, recent studies have shown that the combination of cardiac POCUS and abnormal vital signs can increase the sensitivity to over 95 % for ruling out PE, making cardiac POCUS a useful tool to exclude significant PE in these patients. The presence of a normal tricuspid plane systolic excursion (TAPSE) in a patient with suspected PE and tachycardia can essentially exclude PE as a diagnosis (49). Other studies have shown improved diagnostic test characteristics by combining deep vein thrombosis (DVT) assessment with POCUS to increase sensitivity (50-52).

McConnell's sign, the finding of hypokinesis or akinesis of the RV free wall with preserved apical motion, can also help determine right heart strain, and is thought to be associated with acute strain as opposed to chronic strain (53,54). This finding has previously been shown to be highly specific for PE, with some literature demonstrating a specificity approaching 100 % (45,55). However, the high specificity of McConnell's sign has been called into question recently. Case reports have demonstrated McConnell's sign in patients with pulmonary hypertension from other underlying conditions, in cases of RV ischemia or infarction, or those with acute chest syndrome (56-59). Thus, McConnell's sign does not exclude the presence of pathologies other than PE.

Given the limitations of using an abnormal RV:LV ratio as the sole diagnostic evaluation for PE, more recent POCUS literature evaluated the significance of other echocardiographic findings of acute RV dysfunction. TAPSE uses M-mode at the lateral tricuspid valve annulus to measure dynamic movement and generate a wave of movement that can be measured from peak to trough; the value of < 17 mm is considered abnormal (Figure 4). TAPSE can be performed with high interobserver reliability amongst emergency physicians (50,60,61). One pitfall of TAPSE is the need for good visualization of the lateral RV wall, which can be difficult in some patients. Improving patient positioning with the left arm raised above the head and a left lateral decubitus tilt can sometimes improve image quality.

Lastly, the 60/60 sign is another sonographic sign for PE that has had increasing interest in determining the presence of acute RV dysfunction. This is found by determining both the TR pressure gradient and the pulmonary acceleration time; a finding of ≤60 mmHg and ≤60 ms, respectively, in a patient being evaluated for PE has high specificity though low sensitivity (60,62). The 60/60 sign requires the presence of TR and the use of color Doppler and pulsed wave Doppler, making it a more advanced calculation, but can help to differentiate between acute and chronic RV strain (60,62).

Exit

Measuring the aortic outflow tract (AOFT) diameter, or "exit," is an essential component of cardiac POCUS and is effectively visualized in the PSLA, providing an excellent depiction for accurate measurement and diagnosis of

ascending aortic aneurysm. Although visualizing an intimal flap could directly indicate aortic dissection, AOFT dilation has been associated with a high risk of major adverse aortic events, such as dissection (63). The initial approach of the 5 Es recommended measuring from the leading edge to the leading edge, spanning from the outer wall to the inner wall (OTI) in the PSLA view (3). Notably, this proposed approach demonstrated a strong correlation with inner-edge to inner-edge measurements obtained from CT, further supporting its accuracy and clinical relevance in suspected patients (64). Although a normal AOFT diameter cannot rule out aortic dissection, nor can its dilation confirm the diagnosis, the significance of cardiac POCUS in improving the time to diagnosis is noteworthy, given a reduction of 146 minutes in patients with aortic dissection who received cardiac POCUS as an initial diagnostic test (65). In particular, the presence of a dilated AOFT in combination with a pericardial effusion is highly suggestive of a type A dissection.

The upper limit of normal for the AOFT has been subject to additional research. The diameter of ≥ 4 cm in PSLA view with the OTI method showed a sensitivity and specificity ranging from 59.6 % to 78.6 % and 85.4 % to 92.9 %, respectively, for acute aortic syndromes (66,67). A more recent study by Gibbons et al. utilized a lower cutoff of 3.5 cm and yielded a sensitivity of 100% and specificity of 91.8 % for the diagnosis of aortic dissection (68). While this study had a strong sensitivity and specificity, the positive predictive value (PPV) for this method was notably low (16.8 %) given the amount of patients without an aortic dissection who ruled into the study based on the AOFT measurement alone. Notably, this study utilized an inner-to-inner (ITI) method of measurement, so a higher cutoff would be needed for the more widely accepted OTI measurement technique (69,70). We continue to recommend the use of the OTI measurement, with < 4 cm as normal, 4.0 – 4.5 cm as borderline, and ≥ 4.5 cm as dilated for the AOFT measurement as discussed in the original article (3).

With the rise in AI and machine learning algorithms in POCUS, the AOFT measurement may be automated in the future, although no current real-time measurement tool is commercially available at this time.

Entrance

The IVC is best visualized by finding the subxiphoid cardiac view and then rotating the probe indicator towards the patient's head, rocking inferiorly to center the liver in the screen, and then sliding to the patient's right (3). The main use of the IVC in POCUS is to assess for volume status, with measurement of the IVC at end expiration ≥ 2 cm considered plethoric (volume overload), and < 1 cm considered flat (volume depletion). This measurement can be performed by freezing the image or using M-mode over a respiratory cycle. This measurement's usefulness is highlighted by its ability to noninvasively estimate right atrial pressure (RAP). A plethoric IVC > 2 cm suggests a pathologic RAP > 8 mmHg, whereas a plethoric IVC with less than 50 % collapse suggests a RAP > 15 mmHg (71).

IVC assessment is also important in assessing right ventricular systolic pressure (RVSP). RVSP can be calculated if the patient has TR on color flow Doppler (CFD). In the presence of TR, continuous wave (CW) spectral Doppler can estimate the RV pressure gradient using peak TR velocity (V), which is then added to right atrial pressure (RAP) using the formula RVSP = $4V^2$ + RAP. RVSP can be elevated acutely in PE, or chronically in pulmonary hypertension (72).

In recent years, the accuracy of IVC measurement has been called into question and can be limited by clinical scenarios such as the cylinder tangent effect of being off-axis of the IVC, a chronically dilated IVC, pediatric limitations, TR, RV failure, COPD exacerbations, pregnancy, obstructive shock, mechanical ventilation, etc (73). To avoid some of these limitations, there has been increasing research into the other surrogates for measuring volume status such as the Venous Excess Ultrasound (VExUS). VExUS is applicable when the IVC is ≥ 2 cm, and uses both hepatic vein Doppler, portal vein Doppler, and renal vein Doppler to determine whether the patient is volume overloaded (74-76). VExUS, or portions of the VExUS assessment, are being investigated as more accurate ways to assess volume status.

The assessment of right ventricle dilation via the RV:LV ratio helps identify conditions like pulmonary embolism and right heart strain. Advances in POCUS, such as TAPSE and the 60/60 sign, enhance diagnostic accuracy for right heart dysfunction.

Tools have been developed to automatically measure the IVC and its collapsibility using AI (7,77). This tool is mostly useful for the novice operator, as previous studies have shown that experienced operators have moderate to good interrater reliability for visual estimation of IVC measurement and collapse (78).

Discussion and Future Directions

Cardiac POCUS can be incredibly useful in the evaluation of the acute patient presenting with chest pain, dyspnea, hypotension, or syncope. However, it can also be challenging to distill what information is needed and important. The 5 Es are an attempt to distill down the potential findings into a manageable protocol that will identify the most important emergent findings. We specifically excluded detailed valvular assessment as it is typically beyond the

scope of POCUS, though this does not mean that POCUS could not identify significant or obvious valvular pathology.

In this review we have highlighted some techniques related to the 5 Es including use of m-mode and Doppler that may be more advanced than some users are comfortable with. Our intent is to review and reinforce the 5 Es while providing some additional techniques and considerations for those who are comfortable with basic cardiac POCUS evaluation, and to bring up other possibilities for augmenting evaluation. These techniques are not always necessary, and each sonographer should use approaches that they are comfortable with.

The advent of AI is exciting and touched on in this paper. A future can be imagined where relatively novice users are guided through image acquisition and interpretation with good accuracy. However, we are far from the point where AI will replace an experienced sonographer. The effective use of cardiac POCUS requires knowing when to use it, how to acquire good images, interpretation of these images, and incorporation of findings into diagnosis and clinical care. The full scope of doing this in an automated manner is not something that is on the immediate horizon.

The acquisition of cardiac images can be challenging and there are some AI solutions in this space. In 2020, the United States Food and Drug Administration (FDA) approved the first system to help guide a user in image acquisition for cardiac POCUS (79). There are an increasing number of publications that purport to demonstrate reliability and accuracy of interpretation. However, many of these algorithms remain proprietary and are not available for evaluation and general use. Ultrasound manufacturers are rapidly trying to develop and deploy AI, however, this requires the purchase of equipment or software with this capability, and each of these algorithms may be slightly different.

In the United States, the FDA regulates the use of devices for medical diagnosis. While the quantification of certain parameters (for example EF or IVC diameter) is more straightforward and these devices are in use, the threshold for approval of an actual diagnosis (such as "tamponade") is a much higher bar.

Perhaps one of the more immediate applications for AI will be in education and quality assurance. It is quite feasible in the near future that AI will be able to "flag" examinations for review where the interpretation rendered by a less experienced user is discrepant from the AI interpretation. This can streamline review by more experienced sonographers to provide valuable feedback. AI could also be helpful in identifying cases on a large scale for research purposes.

The potential for more "open-source" or "open-access" AI has yet to be realized. While commercially available solutions are increasing, they come with cost and the need to evaluate and use each solution separately with proprietary equipment. Many academic institutions are developing AI solutions that would benefit from more widespread dissemination that allow testing and applications on local data. We look forward to a future when there is freely available and generally applicable AI solutions in this space. It is possible that a Chat-GPT like model for medical imaging may be developed at some point.

Conclusion

Cardiac POCUS remains an essential tool in the evaluation of the acutely ill patient, and the 5 Es provide a framework for identifying important pathology. In this review we hope to emphasize the 5 Es and highlight refinements and additional methods for evaluation, but the underlying physiology and pathology remain the same. Artificial intelligence is developing rapidly, but the need for sonographers who can effectively obtain, interpret, and integrate cardiac POCUS into the care of their patients is still paramount.

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REVIEW ARTICLE / PREGLEDNI ČLANAK

DELIRIUM ASSESSMENT AND MANAGEMENT IN EMERGENCY DEPARTMENT

PRISTUP I LIJEČENJE DELIRIJA U HITNOM BOLNIČKOM PRIJEMU

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Abstract

Delirium is an acute, in most cases reversible syndrome, primarily characterized by qualitative disorders of consciousness and disorders of higher cognitive functions. Recognition and assessment of delirium is of utmost importance in acutely and critically ill patients, as it carries significant morbidity and mortality. In the clinical environment, we identify delirium mainly amongst the population of elderly, fragile patients. It can cause complications in the course of treatment, which can further worsen the patient's physical and mental condition and is often the cause of poor prognosis and treatment outcomes, including death. Recognizing delirium enables rapid initiation of treatment, which is associated with better outcomes.

Keywords: delirium; acute encephalopathy; acute confusion; emergency department

Sažetak

Delirij je akutni, u većini slučajeva reverzibilni sindrom, prvenstveno karakteriziran kvalitativnim poremećajima svijesti i poremećajima viših kognitivnih funkcija. Prepoznavanje i procjena delirija od iznimne je važnosti kod akutnih i kritičnih bolesnika, budući da nosi značajan morbiditet i mortalitet. U kliničkom okruženju delirij identificiramo uglavnom među populacijom starijih, krhkih bolesnika. Može uzrokovati komplikacije u tijeku liječenja, što može dodatno pogoršati tjelesno i psihičko stanje bolesnika te je često uzrok loše prognoze i ishoda liječenja, uključujući i smrt. Prepoznavanje delirija omogućuje brzo započinjanje liječenja, što je povezano s boljim ishodima.

Ključne riječi: delirij; akutna encefalopatija; akutna smetenost; hitni bolnički prijem

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Introduction

Delirium is an acute mental disorder, characterized by a disturbance of consciousness (qualitative), a fluctuating course and disorders of higher cognitive functions (disorders of orientation, memory, thinking and behavior). It develops over a short period of time (hours, days) and has a tendency for symptoms to vary throughout the day (1,2).

In the 11th revision of the ICD (International Classification of Diseases), delirium is defined as an etiologically non-specific organic cerebral syndrome that has the following characteristics:

- disturbance of consciousness and attention,
- global cognitive disorders (illusions, hallucinations, thought disorders, memory disorders, recall problems, disorientation...),
- psychomotor disorders,
- sleep and wakefulness rhythm disorders,
- emotional disorders (1,3,4).

Hyperactive delirium

Hyperactive delirium is a form of delirium, characterized by state of increased alertness and agitation. It is more often accompanied by hallucinations, delusions, agitation and inappropriate behavior of the patient (1,5).

Prominent psychomotor agitation is characteristic, patients are restless, excited, sometimes even aggressive towards themselves and their surroundings. Reactions to environmental stimuli such as light, touch or noise can be exaggerated. Various inappropriate behaviors occur, such as screaming, removing inserted medical equipment (peripheral and central channels, catheters, sutures...). Patients might have a tendency to flee. Hallucinations and illusions, disorientation and emotional lability are common. Patients act as if they have psychosis but without prodromes (3,5,6).

Hypoactive delirium

Hypoactive delirium is a subtype of delirium, characterized by reduced psychomotor activity, lethargy and reduced response to environmental stimuli, and apathy. This form is often overlooked, as we do not observe clear disturbing behavioral disorders in the patient (3,4).

Clinically, it manifests as psychomotor hypoactivity, patients are sleepy, may be unresponsive, have problems following their surroundings and focusing, are apathetic to their surroundings and interactions with other people. We can observe quantitative disorders of consciousness in the sense of somnolence and stupor, but patients may simply be less oriented in time, space and person. Problems with understanding, memory and judgment also stand out. It occurs more often as a result of somatic diseases. It is especially common in palliative care (3,7,8).

Mixed delirium

Mixed delirium is a combination of both hyperactive and hypoactive delirium. Patients have a combination of symptoms of the two types of delirium listed above, which alternate with each other (2,3).

Delirium due to alcohol withdrawal; *delirium tremens*

We speak of alcoholic delirium as an etiologically special form of delirium, as a severe complication of alcohol withdrawal syndrome. It manifests itself as a hyperactive form. It can occur during actual withdrawal from alcohol or during other conditions (infections, injuries,...) when the patient cannot consume alcohol due to the nature of the problems themselves. It manifests as agitation with confusion and disorientation; hallucinations and autonomic signs such as fever, hypertension, diaphoresis and tachycardia are common. Electrolyte disturbances can lead to rhythm disturbances, epileptic seizures or even sudden cardiac death. It usually lasts 3 to 4 days, but can take up to 10 days (5,9,10).

Delirium in elderly and frail patients

Elderly, frail patients are a high-risk population for the development of delirium, which is often associated with prolonged hospitalization and worse treatment outcomes. It is often difficult to recognize due to overlap with other pathologies of old age, such as dementia and depression. The symptoms are similar to those of other types, manifesting as attention deficit disorder, confusion, disorientation, disturbances of consciousness and behavior. The most common cause of delirium in elderly patients is infection, followed by hospitalization (change of environment) and worsening of underlying chronic diseases (11,12,13).

Delirium in oncologic patients and palliative care

In oncology and palliative care, delirium is a common and serious symptom. It mainly occurs in patients with advanced and end stages of the disease. It can be caused by an underlying disease, but often occurs as a result of treatment (chemotherapy, immunotherapy), associated pharmacotherapy (treatment with opioids), metabolic disorders, infections or dehydration. Treatment of delirium in palliative care focuses primarily on managing symptoms, alleviating suffering and improving patients' quality of life. We use etiological treatment and treatment with medicinal and non-medicinal measures (3,14,15).

Epidemiology of delirium

Data on prevalence of delirium varies from study to study. Delirium should occur in about 10-15 % of all hospitalized patients; it is much more common in those who are older than 65 years, some references report prevalence of more than 50 % of this patient population. The occurrence is also related to hospitalizations, with higher incidence in surgical

wards, where elderly patients are treated after injuries and fractures (even more than 50 %), in intensive care units and in patients hospitalized for a malignant disease. Unrecognized delirium leads to longer hospitalization and higher mortality (3,16,17). According to some studies, delirium remains unrecognized in emergency departments (ED) in approximately 2/3 of cases (17,18).

Pathophysiology and etiology

The exact mechanisms that cause delirium are yet unknown, but it is most likely caused by reversible malfunction of the oxidative metabolism in the brain, responsible for changes in the metabolism of various substances, altered enzyme systems, and a more permeable blood-brain barrier or cell membranes. Disturbed metabolism of neurotransmitters and disturbances in the function of the right hemisphere, necessary for adequate attention, also play a role (3,19).

The pathophysiology of delirium is related to the action of various neurotransmitters; acetylcholine, dopamine, serotonin, gamma-aminobutyric (GABA) and glutamate. Acetylcholine plays an important role in memory, consciousness and attention. Dopamine is associated with disorders of attention, motivation and emotion regulation. Serotonin mainly affects mood (3,20).

Delirium also encompasses impairment of higher brain functions, centred in the cerebral cortex. Delirium development requires the involvement of several neurotransmitter systems, the cholinergic system being particularly important. This is the reason why drugs with anticholinergic properties very often cause delirium. By acting on muscarinic receptors, they affect subcortical cholinergic fibers and thus reduce the flow of neurotransmitters to the cortex and hippocampus. The mechanism of delirium that occurs during withdrawal from benzodiazepines and barbiturates is most likely related to hypersensitivity of GABA receptors. A similar mechanism is also present in delirium of alcoholic etiology (3,19,20).

A higher risk of delirium is present in the elderly and frail patient population. Risk factors that increase the likelihood of delirium are:

- age over 70 years,
- dementia (in many cases it is first diagnosed only later),
- male gender,
- poor eyesight and hearing,
- other associated cognitive disorders (mental retardation, psycho-organic changes),
- (chronic) abuse of alcohol and psychoactive substances,
- metabolic abnormalities (metabolic, electrolyte, elevated inflammatory parameters...) (3,5,19).

Causes of delirium are multiple. In very fragile patients, development of delirium can be precipitated by even a minor disturbance such as lack of sleep, urinary retention, dehydration and constipation. The most common causes are:

- side effects of drugs (psychotropic drugs such as antipsychotics, sedatives, antidepressants and anxiolytics, anticholinergics, opioid analgesics),
- withdrawal from drugs, polypharmacy,
- operative interventions (orthopedic and traumatological interventions in the elderly) and general anesthesia,
- hypoxia,
- pain,
- infections,
- acute diseases and exacerbations of chronic diseases,
- dehydration,
- immobility (3,5,21).

Causes of delirium can be easily remembered by mnemonic "**I WATCH DEATH**" shown in Table 1 (2,3,5).

Table 1. Causes of delirium (5)

Mnemonic	Specific causes
I - nfectious	Sepsis, encephalitis, meningitis, syphilis
W - ithdrawal	Alcohol, barbiturates, sedatives, hypnotics
A - cute metabolic causes	Acidosis, electrolyte disturbances, liver and kidney failure, hypo/hyperglycemia,
T - rauma	Head injuries, burns
C - NS (cerebral nervous sistem) diseases	Cerebral hemorrhage/stroke, vasculitis, convulsions, tumors
H - ypoxia	Acute hypoxia, chronic lung diseases, hypotension,
D - eficiencies (vitamins, micronutrients)	vitamin B12, niacin, thiamine
E - nvironmental factors	Hypo/hyperthermia, endocrinopathies, diabetes, thyroid/adrenal gland diseases
A - cute vascular	Hypertensive crises, SAH, central venous sinus thrombosis
T - oxins/drugs/ medications	Medicines, drugs, alcohol, pesticides, poisons, CO, cyanides
H - eavy metals	Lead, mercury

SAH – subarachnoid hemorrhage; CO - carbon monoxide

Clinical signs and symptoms

Delirium can be heralded by prodromal signs such as restlessness, anxiety, fear, and hypersensitivity to light and sound (1).

The clinical picture develops in few hours to days. Manifestations of symptoms fluctuates over time,

symptoms usually being more pronounced at night (2,3) (old clinical adage, "nights possess special powers").

Patients may experience difficulties with orientation. Orientation in time is most often and first affected (difficulties in determining the part of the day are considered a sensitive indicator of delirium), spatial and personal orientation are less frequently affected (1).

Patients with delirium often have hallucinations; dreams and illusions can be intertwined. Perceptual disturbances are most often optical or auditory. Olfactory and tactile hallucinations occur less frequently. Hallucinations and experiences are often unpleasant, patients are often frightened, tense and anxious. Attention is also disturbed, the flow of thought is slowed down and incoherent (2,3).

Disorders of the autonomic nervous system may occur, such as skin erythema or pallor, sweat, tachycardia, arrhythmias, hypertension, vomiting, mydriasis and hyperthermia. These symptoms often occur in delirium that occurs as a result of withdrawal from alcohol, sedatives and hypnotics (1,2,3).

Memory disorders are present both in terms of difficulty with memorization and recall; patients can fill individual memory holes with confabulations. Patients are typically amnestic for the period of delirium. The rhythm of sleep and wakefulness is often completely reversed, but patients may have problems especially with insomnia (4,22).

The behavior of patients can be very extreme; on one hand, there can be psychomotor retardation, patients can be imperceptible and mutatic, and on the other hand, there can be very pronounced restlessness with loud and rapid speech. Patients can experience emotional disturbances, they can be very irritable and agitated, anxious, and emotionally numb. Depressed mood, confusion and thoughts of suspicion are often associated with delirium (2,3,23).

Diagnostic assesment

Diagnosis of delirium is clinical, suspicion for delirium is mostly based on history by family or caregivers and clinical exam. There are no specific diagnostic tests for delirium and even laboratory tests can only confirm a possible etiological cause of delirium (infection, metabolic disorders, electrolyte imbalance, etc.). To rule out somatic causes, CT and MR imaging can be performed, as also EEG recording of brain activity; these can demonstrate a bilateral, diffuse abnormality of the basic electrical activity with a slowing rate of the average frequency (1,2,3).

To make a diagnosis, we use the DSM-V (Diagnostic and Statistical Manual of Mental Disorders) criteria:

- disturbance in attention and consciousness,
- the disorder occurs quickly (a few hours to few days) and represents a change in patients condition, compared to their baseline behavior and clinical exam,
- disturbance in thinking (i.e. memory, disorientation, disturbances in speech, vision, perception),
- the disorder cannot be explained by another or previously existing neurological deficit,
- there is enough evidence in history, physical examination and laboratory tests that the disorder may be the result of illness, intoxication or withdrawal from a certain substance and a possible side effect) (2,24,25).

The bCAM and 4AT tests are used to help identify delirium, and the CAM-ICU scale is also used in intensive care units (25).

bCAM (Brief Confusion Assessment Method)

bCAM is a delirium screening tool and is a simplified version of the Confusion Assessment Method (CAM). It is adapted for settings where time for assessment limited (emergency centers, intensive care units). It focuses on 4 key features of delirium:

- acuteness of the onset of symptoms (anamnesis and/or hetero-anamnesis on the patient's mental state and changes in the last 24 hours),
- attention disorders,
- disorganized thinking (we ask the patient simple questions such as "*Does a stone float on water*?" and evaluate the logic and appropriateness of the patient's answers),

altered level of consciousness (we assess whether the patient has signs of hypo- or hyperactive delirium - impaired consciousness, lethargy, restlessness, agitation).

The Richmond-Agitation-Sedation-Scale (RASS) is also part of the assessment of delirium according to the bCAM scale. Figure 1 and Table 2 show a brief delirium screening tool; bCAM (26,27,28). bCAM has proven to be a highly specific but less sensitive tool (27).

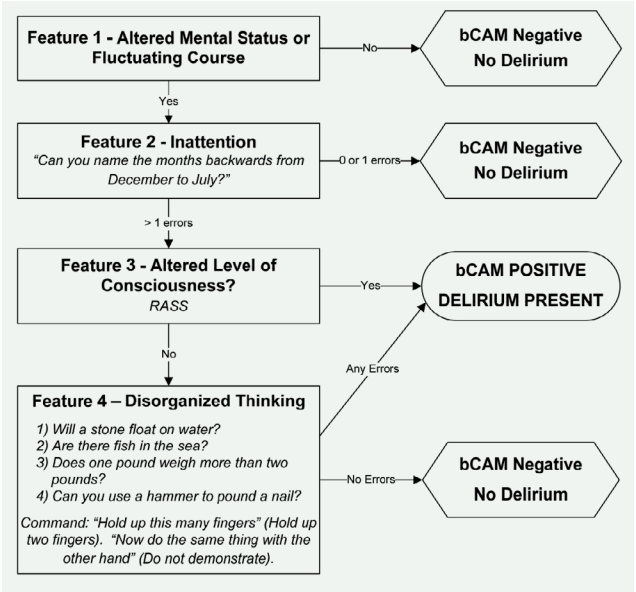

Figure 1. brief delirium screening (bCAM - brief Confusion Assessment Method). Adapted from (28).

Table 2. Richhmond Agitation and Sedation Scale, RASSS. Adapted from 28.

RASS	Description
+4	Overtly combative, violent, immediate danger to staff
+3	Very agitated, pulls or removes tube(s) or catheters); aggressive
+2	Agitated, frequent non-purposeful movement
+1	Restless, anxious but movements not aggressive or vigorous
0	Alert and calm
-1	Mildly drowsy, not fully alert, but has sustained awakening (>10 seconds)
-2	Moderate drowsy, briefly awakens with eye contact to voice (<10 seconds)
-3	Very drowsy, movement or eye opening to voice (but no eye contact)
-4	No response to voice , but movement or eye opening to physical stimulation
-5*	No response to voice or physical stimulation

4A test

The 4A test is a simple and rapid screening test, suitable for use both in emergency departmets and other settings. We assess the patient's alertness, acute onset and fluctuation of symptoms, attention and memory, and cognitive impairment. In research, the test has shown high diagnostic accuracy. Table 3 shows how 4AT test is performed (27,29,42).

Differential diagnosis of delirium

Delirium is a condition characterized by acute and reversible disturbances of consciousness and cognition, and may also be accompanied by various neuropsychiatric symptoms. For appropriate managament and treatment, delirium must be recognized and distinguished from other similar conditions. We establish the diagnosis with a systematic auto or hetero-anamnesis (history), a detailed clinical examination, aided by laboratory and imaging tests. The most common differential diagnosis (alternative causes) are:

- dementia (both conditions are characterised by cognitive impairment; delirium, unlike dementia, occurs acutely and fluctuates in time. Dementia is chronic, progressive disease),
- depression (in both conditions, apathy and cognitive problems can be observed, in depression there should be no acute changes in consciousness),
- psychosis (hallucinations may occur in both cases, consciousness should not be disturbed in psychosis or any other "pure" psychiatric disease),
- stroke (both conditions can have a sudden onset with confusion; in stroke we generally observe focal neurological deficits, in delirium it is a diffuse impairment without clear lateralization),

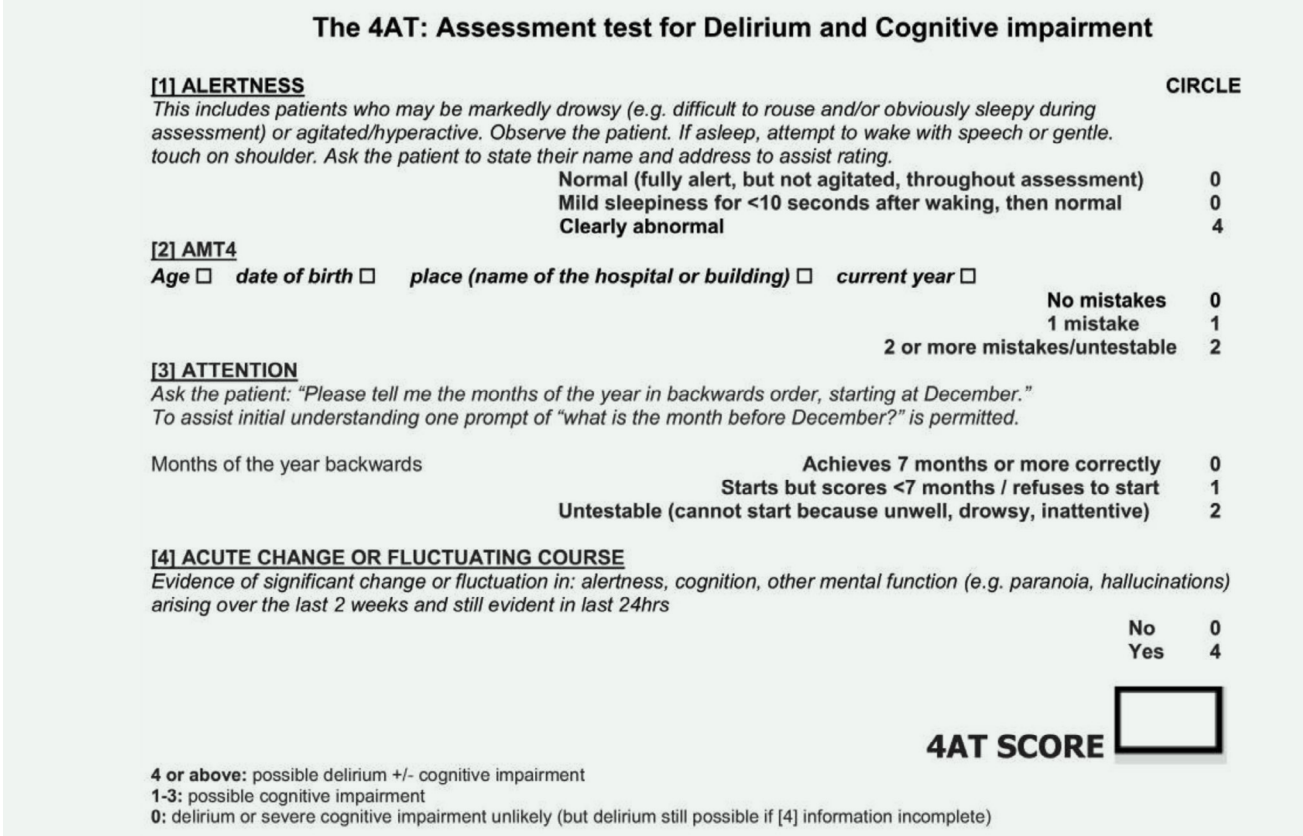

Figure 2. 4 A test. Adapted from 42.

- electrolyte and metabolic disorders (hypoglycemia, hypo/hypernatremia, hypoxia/hypercapnia), endocrinological conditions (hypo/hyperthyroidism, Addison's crisis),
- sepsis,
- drug poisoning,
- intoxication with alcohol or other psychoactive substances,
- expansive lesions of the brain (tumors, hydrocephalus, hemorrhages, ...) (3,18,31).

Delirium is an acute mental disorder, characterized by a qualitative disturbance of consciousness, a fluctuating course and disorders of higher cognitive functions such as disorders of orientation, memory, thinking and behavior.

Delirium management in emergency department

In emergency departments, doctors and other health-care providers often encounter delirium, so recognizing it is very important. We approach patient with possible delirium as any other patients in emergency medicine: primary (ABCDE) and secondary exam and in parallel obtain history from patients and caregivers, which is usually key to identifying changes in patient's behavior. We supplement diagnostic assessment with laboratory and imaging tests, trying to identify the triggering factor of delirium. bCAM and 4AT tests can be used for screening and confirmation of diagnosis (31,32,33).

After establishment of a diagnosis, urgent causative etiologic treatment is the cornerstone of delirium management. Medications (antipsychotics and benzodiazepines) are used to control symptoms, not to treat the root causes of delirium (3).

Regarding elderly and fragile patients, we will also discuss plans for further treatment and safety, or appropriateness of hospitalization.

Treatment of delirium

Treatment of delirium is primarily etiological. By treating the underlying cause, symptoms of delirium may be reversed accordingly. In parallel, we must stabilize patients, provide them with cognitive support, and in most cases, also use supportive pharmacological treatment (3).

It is therefore of utmost importance to recognize delirium identify and treat its cause, to provide patients with an appropriate environment and support, and to use medication when necessary, while continuously monitoring the patient (34,35).

Non-pharmacologic treatment

It is necessary to provide patients with comfort, rest, and sufficient hydration and nutrition. Encouragement is needed in terms of location, time and personal orientation (clock, calendar, family photos, etc.). We should also encourage patients to use eyeglasses or hearing aids.

It is necessary to provide patients with a calm, familiar environment and to reduce noise. We should try to maintain a daily routine, paying special attention to sleep hygiene and rest. With physiotherapy and walking aids, we should try to mobilize patients as much as possible. Patients should also be provided with spiritual support as needed (33,36).

Pharmacologic treatment

The choice of medication depends on predominant symptom phenotype. Pharmacologic therapy with antipsychotics or benzodiazepines is not causal, but merely symptomatic. The pathophysiological mechanism of delirium hinges on imbalance between neurotransmitters, mostly with an excess of dopaminergic transmissions and a lack of cholinergic transmissions. Medication treatment is also based on this principle (3,37).

Haloperidol is an effective medication in most patients (except for withdrawal syndrome and poisoning with anticholinergics). We mainly use antipsychotics with predominantly hyperactive form, with symptoms of aggression, agitation and hallucinations:

- haloperidol (Haldol) – often used due to its fast-acting nature and favorable safety profile in short-term treatment,
  - mild to moderate delirium: 0.5 - 3 mg intramuscularly or orally every 8 - 12 hours and every 1 hour if necessary. When a dose needs to be titrated, use 50 % of the daily dose, which is divided into up to 3 daily doses,
  - pronounced delirium with agitation: 1.5 - 3 mg intramuscularly or orally every 8 - 12 hours, up to a maximum daily dose of 30 mg,
- quetiapine (Kventiax®, Seroquel®)
  - 12.5 – 50 mg per 12/24 hours up to a maximum daily dose of 200 mg,
- olanzapine (Zolrix, Zyprexa)
  - 1.25 - 5 mg/24 hours orally or 2.5 - 5 mg/day intramuscularly up to a maximum daily dose of 20 mg,
- risperidone (Torendo, Rispolux)
  - 0.25 - 2 mg orally, can be repeated every 2 hours up to a maximum daily dose of 6 mg.

Antipsychotics are prescribed in a lowest effective doses and are gradually discontinued when delirium subsides. Side effects manifest mainly due to their cholinergic effects, namely dry mouth, dizziness, headache, constipation, increased appetite and tachycardia (37,38).

For treatment of delirium tremens (severe alcohol withdrawal), clomethiazole (Hemineurin/Distraneurin) is most commonly used in Europe. It has hypnotic, sedative and anticonvulsant effects. Doses range between 200 - 400 mg, which can be repeated after one hour, and then every 2 - 3 hours, up to a maximum daily dose of 2 g. It is not recommended to use in intoxicated patients, as the drug can further suppress the central nervous system. When used for more than 10 days, addiction may develop, and side effects are mainly on the nervous system (respiratory center depression, drop in blood pressure). Some recent studies have also described the use of phenobarbital in patients with withdrawal symptoms, where better clinical outcomes were observed with the use of phenobarbital compared to monotherapy with benzodiazepines (37,39,40).

We also use benzodiazepines, with short half-life. They can be used in combination with antipsychotics for cases of severe hyperactive delirium. We most often use:

- oxazepam,
  - 10 - 30 mg 3 - 4 times a day,
- midazolam (Dormicum),
  - 2.5 - 5 mg orally or intravenously, up to a maximum of 15 mg in 24 hours,
- lorazepam (Loram)
  - 0.5 - 1 mg 1x/day orally, 1 - 2 mg intramuscularly,
- diazepam
  - 2 - 5 mg orally, 5 – 10 mg intravenously plus repeat if necessary.

According to some studies, delirium remains unrecognized in emergency departments in approximately 2/3 of cases. Unrecognized delirium leads to longer hospitalization and higher mortality.

Benzodiazepines play a role in the symptomatic treatment of delirium, especially in patients with hyperactive delirium, delirium in terminally ill oncology patients, and delirium during alcohol withdrawal. We must also be aware of side effects, which in the case of benzodiazepines are mainly confusion and agitation, and in case of overdose, respiratory depression, hypotension, nausea and vomiting may also occur (14,39,41).

In treatment of hypoactive delirium, benzodiazepines are avoided, the use of antipsychotics in low doses is recommended, atypicals are preferred (14,15,37).

Equally, prevention of delirium is critically important; this includes timely causal treatment of the disease, care for adequate hydration and nutrition, reduction of unnecessary hospitalizations and transports to emergency departments, reduced use of drugs that cause delirium and provision of a stimulating environment with social interactions (39).

In most patients, prognosis depends on cause of delirium; in general worse treatment outcomes are associated with older age, frailty, hypoactive delirium and longer duration of delirium. Literature reports hospital mortality of patients with delirium up to 18%, which is almost twice as high as in the population without delirium (3,4).

Summary

Delirium is a clinical syndrome of acute confusion and other cognitive disturbances, caused by a number of different factors and has a heterogeneous clinical picture. The main characteristic is a qualitative disturbance of consciousness, which in most cases is the result of other medical conditions. Delirium is generally divided into hypoactive, hyperactive and mixed types. Delirium is today highly prevalent in ED, especially in elderly, fragile and oncologic patients. Establishing a correct diagnosis can be challenging, and it is often overlooked, resulting in worse outcomes and increased mortality. Treatment is based on reversing the somatic cause, aided by symptom control with antipsychotics or benzodiazepines, and other non-pharmacologic and supportive measures.

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REVIEW ARTICLE / PREGLEDNI ČLANAK

ULTRASOUND IN EMERGENCY MEDICINE

ULTRAZVUK U HITNOJ MEDICINI

*** Radovan Radonić**[1]

Abstract

Ultrasound is increasingly becoming an indispensable method and a fundamental tool in emergency medicine as it allows direct visualization of organs and organ systems, providing the attending physician with a better understanding of the patient's pathophysiological processes compared to relying solely on history and physical examination.

Key words: ultrasound; emergency medicine; point-of-care ultrasound (POCUS)

Sažetak

Sažetak

Ultrazvuk sve više postaje neizostavna metoda i osnovni alat u hitnoj medicini budući da omogućava izravnu vizualizaciju organa i organskih sustava, te liječniku koji zbrinjava hitnog bolesnika omogućava kvalitetniji uvid u patofiziološke procese bolesnika, nego što bi bilo samo na temelju anamneze i fizikalnog pregleda.

Ključne riječi: ultrazvuk; hitna medicina; ultrazvuk uz krevet bolesnika

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Introduction

Ultrasound enables visualization of the body's interior, thus providing insight into the morphology and function of internal organs. Unlike radiological methods, it does not involve ionizing radiation, and examinations can be conducted without harmful side effects for either the patient or the examiner. Portable compact devices make it accessible at the examination site, including pre-hospital emergency medicine. In the hands of a trained emergency physician, ultrasound offers immediate and valuable information about the patient, facilitating a quicker and more accurate assessment of their condition, guiding further diagnostics and treatment.

Ultrasound entered emergency medicine through targeted partial training for emergency physicians in ultrasound use, with protocols developed for specific situations. One of the first such protocols is the FAST protocol, designed for trauma patients at risk of internal bleeding, requiring immediate surgical intervention (1-10). Waiting for a specialist qualified in ultrasound examination can delay intervention, jeopardizing the patient's health and life. Free fluid in body cavities lined with serosa accumulates in typical locations and, if present, is easy to identify via ultrasound. Training physicians to perform the FAST protocol accelerates the identification of internal bleeding. Other ultrasound examination protocols, such as RUSH and BLUE, have also been developed for specific emergencies (11,12).

However, we advocate a holistic approach to ultrasound use in emergency medicine, encompassing basic-level whole-body ultrasound tailored to the clinical scenario. This involves using ultrasound to address clinical questions arising during patient management. Such examinations are a logical extension of the clinical evaluation of emergency patients, where the sequence and thoroughness are adapted to the situation and time constraints. Typically,

this includes a rapid lung assessment, focused cardiac examination, evaluation of circulatory system volume status by assesment of inferior vena cava diameter, a quick abdominal examination including the abdominal organs, kidneys, abdominal aorta, and other structures. Diagnosing venous thrombosis is also a frequent clinical question in emergency medicine that ultrasound can address. Data obtained are immediately integrated into the clinical reasoning process, and existing patient information can sometimes aid in interpreting ultrasound findings. Ultrasound is also highly useful for performing certain invasive procedures.

Professional societies support clinician-performed ultrasound by developing guidelines and providing structured education. Ultrasound training is now integrated into medical school curricula and is a mandatory part of specialty training in emergency medicine and other fields.

French intensivist Daniel Lichtenstein significantly contributed to this field, conceptualizing principles of "visual medicine" based on ultrasound's role in clinical patient management (13). The development of this field has also been driven by the World Interactive Network Focused On Critical UltraSound, (WINFOCUS), organization, which has structured education suitable for emergency ultrasound use and developed a network of training centers offering licensed courses for clinicians worldwide, including in Croatia (14). National and international professional societies recognize the benefits of clinician-performed ultrasound and contribute by proposing guidelines and organizing structured education (15). Ultrasound training for clinicians is increasingly integrated into medical school curricula and has become a mandatory component of specialty training in emergency medicine and other clinical disciplines (16).

Although ultrasound is a relatively simple diagnostic method that clinicians can master, it is essential to distinguish between comprehensive ultrasound examinations by highly trained sonographers under optimal conditions and emergency ultrasound by clinicians with basic short-term training performed under time constraints, suboptimal conditions, based only on visual impressions, without measurements. Awareness of the method's limitations and one's competencies is crucial, using ultrasound as an aid in clinical reasoning in emergency medicine. Ultrasound findings should be verified with consultative examinations or complementary methods when reliability is in question. Initial doubts about one's competence should not hinder the use of ultrasound, even during early learning phases, provided critical judgment is applied in decision-making based on ultrasound findings.

Lung Ultrasound

Daniel Lichtenstein's most significant scientific contribution lies in the development of the concept of lung ultrasound, a groundbreaking advancement that has revolutionised bedside diagnostic approaches and expanded the role of ultrasound in medicine. Beyond classical applications such as diagnosing pleural effusions and lung consolidation, this approach allows the identification of other pathological processes in the lungs (17-20).

Lungs contain air, a medium with acoustic properties vastly different from soft tissues, making it impossible to visualize the structure of lung parenchyma. However, conclusions about pathological processes in the lung parenchyma can be drawn based on artefacts originating from the lung surface. Essentially, two simple questions need to be answered: whether pleural line sliding is observed and whether reverberation artefacts in the form of A-lines or B-lines are present. Based on the combination of findings, the aetiology of acute dyspnoea can be correctly identified in 90% of cases using ultrasound alone (12).

A normal lung finding includes pleural line sliding synchronously with breathing and the presence of A-lines. A-lines are hyperechoic artefacts, parallel to the pleural line, equidistant from it and from each other, corresponding to the thickness of the thoracic wall. They result from multiple reflections of the ultrasound wave between the air-filled lung surface and the ultrasound probe. A shift in the air-to-liquid ratio in the lungs favouring liquid can disrupt the continuity of air on the lung surface. This disruption reduces the surface's "ultrasound mirror" effect, locally preventing reflection and reverberation of ultrasound waves between the lung surface and the probe. Instead, the ultrasound wave penetrates beneath the pleural level into small subpleural areas with water-like acoustic characteristics. Surrounded by air, these areas reflect ultrasound waves internally, creating repeated echoes that generate B-lines on the ultrasound screen (21-24).

Conditions for the formation of B-lines usually first arise in the interlobular septa. As interstitial fluid increases, conditions for small subpleural reverberations expand. B-lines most commonly indicate an excess of extravascular lung water. The appearance of 3–4 B-lines per intercostal space, with the ultrasound probe positioned craniocaudally, suggests oedema of the interlobular septa and interstitial lung oedema, known as the B1 pattern or B1 profile. Five or more B-lines per intercostal space or confluent B-lines indicate a larger amount of interstitial fluid, suggesting partial alveolar filling with fluid. This is referred to as the B2 pattern or B2 profile.

When alveoli are completely filled with fluid, the ultrasound wave can propagate through the lung parenchyma. In cases of lung consolidation (C-pattern or C-profile), the structure of the lung parenchyma becomes visible. In addition to air bronchograms, focal changes otherwise unvisualisable

in air-filled lungs, unless they are subpleural, may be visualized with ultrasound. Similar findings occur with air resorption in obstructive atelectasis. In cases of airway obstruction, diaphragmatic effort does not translate into lung expansion, resulting in the absence of pleural line sliding. Minimal pleural line movement synchronous with the pulse may be observed due to heart-induced lung motion (25). The extent of air resorption determines whether an A-pattern or B-pattern is detected with ultrasound, while complete atelectasis appears as lung consolidation. In cases of obstructive atelectasis, a static air bronchogram is observed, in contrast to the dynamic bronchogram found in conditions involving alveolar exudation (26).

Daniel Lichtenstein's major scientific contribution is the development of lung ultrasound, which has revolutionized bedside diagnostics. This technique, beyond diagnosing pleural effusions and lung consolidation, enables the identification of various other lung pathologies.

Diffuse bilateral homogeneous B-lines are seen in patients with pulmonary oedema caused by fluid transudation from pulmonary capillaries under increased hydrostatic pressure, typically due to hypervolemia and impaired left ventricular function (23). Another cause of fluid entering the lung interstitium is increased capillary permeability at sites of inflammation. Ultrasound is superior to chest X-rays for pneumonia diagnosis (27-35). Bilateral extensive lung infiltrates are characteristic of patients with ARDS. Morphological differences between ARDS and cardiogenic pulmonary oedema can be summarised as follows: cardiogenic pulmonary oedema typically exhibits homogeneity due to uniform transudation into the lung interstitium, whereas ARDS demonstrates an inhomogeneous distribution of extravascular lung water, with preserved areas and regions of greater fluid accumulation (36). Using ultrasound, the severity of inflammatory pulmonary oedema can be semi-quantitatively assessed, aiding in monitoring ARDS patients. Dividing the lungs into regions and scoring each region based on estimated extravascular lung water allows a cumulative LUS score to evaluate therapeutic efficacy (37).

Absence of pleural line sliding, combined with its lack of movement synchronous with cardiac activity, raises suspicion of pneumothorax. Confirmation of pneumothorax requires identification of its boundary (38). When pleural line sliding is absent in the anterior chest of a supine patient, the probe is moved laterally to locate the lung point, marking the boundary of the pneumothorax. The lung point delineates the area where free air separates the pleura, causing a lack of pleural line sliding, from the zone where the lungs contact the thoracic wall, exhibiting pleural line sliding (39). This point typically shifts during the respiratory cycle as pneumothorax boundaries move with inhalation and exhalation. Its detection is 100% specific for pneumothorax as the cause of absent pleural line sliding, ruling out other conditions like obstructive atelectasis or pleural adhesion due to fibrin or connective tissue. Adding pneumothorax diagnosis to the FAST protocol is referred to as the extended FAST or e-FAST protocol.

Focused Cardiac Ultrasound

Focused cardiac ultrasound (FoCUS) involves imaging the heart in typical planes (subcostal view from the epigastrium, parasternal, and apical views), where systolic function of the left ventricle, signs of right ventricular overload (dilatation of the right ventricle with septal displacement to the left), and the presence of pericardial effusion are assessed without measurements, based on "eyeballing." The significance of a pericardial effusion is evaluated by the patient's clinical condition and by the ultrasound finding of chambers collapse (40).

Assessment of volume status based on the diameter of the inferior vena cava and its changes during the respiratory cycle may be imprecise due to multifactorial influences on its size, including the patient's breathing pattern, right ventricular function, intra-abdominal pressure, measurement errors, and other factors (41-43). Despite these limitations, it provides a better insight than clinical estimation of volume status, and findings inconsistent with clinical expectations can help provide a more comprehensive understanding of the patient and their hemodynamics. Recently, venous congestion assessment has been expanded to include Doppler analysis of flow through the hepatic and portal veins and intrarenal veins via the VExUS protocol (44).

Venous Thromboembolic Disease

Venous thromboembolic disease is a common concern in emergency medicine. Clinical symptoms of deep vein thrombosis are unreliable. Ultrasound is the diagnostic method of choice for venous thrombosis (45-47). Instead of the normal anechoic lumen of the vein, which can be fully compressed by probe pressure, venous thrombosis is identified by hyperechoic content corresponding to the thrombus. Compression testing should be performed cautiously to avoid precipitating thrombus migration, and the absence of compressibility should suffice as evidence. It is most critical to examine the veins of the thigh and popliteal region, as these are the most common sources of pulmonary embolism. The veins of the lower leg, as well as the veins of the arms, neck, and inferior vena cava, are also accessible.

Ultrasound in Shock or During Cardiopulmonary Resuscitation

In hemodynamically unstable conditions, shock, or cardiac arrest, point-of-care ultrasound can be pivotal in guiding appropriate treatment (48). Various ultrasound protocols adapted for cardiopulmonary resuscitation settings exist, including FEEL, FEER, CAUSE, PEA, and SESAME (49-54). It is crucial to ensure that ultrasound use does not compromise resuscitation procedures, with usage limited to the time designated for pulse checks in resuscitation protocols. Besides providing a more straightforward and reliable assessment of cardiac function than pulse palpation, ultrasound can identify potentially reversible causes of arrest, such as cardiac tamponade, hypovolaemia, pneumothorax, and suspected thromboembolic events.

A fundamental understanding of shock pathophysiology is essential for directing treatment effectively. Ultrasound can identify the components of the circulatory system responsible for shock, informing treatment strategies. For instance, in cardiogenic shock caused by left ventricular systolic dysfunction, fluid resuscitation is not beneficial but harmful, particularly when pulmonary congestion is present (as indicated by diffuse bilateral B-lines). In contrast, fluid resuscitation is a key treatment step in hypovolemic, septic, and some other shock states. A simple and practical ultrasound-based approach for guiding fluid resuscitation is the FALLS protocol, which suggests halting fluid resuscitation at the first appearance of diffuse B-lines in the lungs (55,56). This is especially suitable for patients with left ventricular systolic dysfunction, as fluid resuscitation is stopped upon achieving optimal left ventricular filling pressure, avoiding pulmonary oedema due to congestion. The protocol is not suitable for those with impaired right ventricular function.

Besides providing a more straightforward and reliable assessment of cardiac function than pulse palpation, ultrasound in cardiorespiratory arest can identify potentially reversible causes of arrest, such as cardiac tamponade, hypovolaemia, pneumothorax, and suspected thromboembolic events.

Shock caused by pulmonary embolism is accompanied by signs of acute right ventricular dilatation and an enlarged inferior vena cava. Lung findings typically show an A-line pattern due to reduced pressure in the pulmonary capillaries, resulting from compromised blood flow to the lungs. Other findings suggesting acute cardiac stress include tricuspid regurgitation, McConnell's sign, visualisation of thrombi in the right heart, early systolic notching in the right ventricular outflow tract, and more (57,58).

The finding of an abdominal aortic aneurysm in the emergency department in a patient with abdominal pain and hypovolemic shock primarily suggests a potential rupture. While the resulting retroperitoneal haematoma may or may not be clearly visible on ultrasound, directing the patient to urgent MSCT aortography will provide all necessary answers before likely urgent intervention.

Ultrasound in shock and cardiopulmonary resuscitation can also assist significantly with airway establishment, vascular access, and management of conditions such as cardiac tamponade, pneumothorax drainage, and more.

Abdominal Ultrasound

Examination of abdominal organs can be useful in the emergency department, especially in patients presenting with abdominal pain (59,60). It allows for easier and more precise assessment of liver and spleen size compared to physical examination, providing valuable information about parenchymal structure and the presence of any focal lesions. Ultrasound is the primary method for diagnosing cholelithiasis and acute cholecystitis (61-63). It can also indicate dilation of the extrahepatic and intrahepatic bile ducts. Although it is not the first-choice method for examining the gastrointestinal tract, ultrasound findings can be striking in cases of severe bowel inflammation with wall thickening and increased fluid content or in cases of ileus. Ultrasound can easily detect free abdominal fluid, which should be interpreted in the context of clinical presentation, and, if necessary, samples can be taken for analysis, facilitated by ultrasound guidance. In addition to free abdominal fluid, free air can also be identified, which may suggest gastrointestinal perforation. The use of ultrasound in diagnosing acute appendicitis requires specific expertise and is not part of the basic ultrasound examination that supplements physical examination (64).

Ultrasound enables visualisation of kidney morphology. It can reliably answer whether there is dilation of the renal collecting system. Assessment of kidney size, parenchymal thickness, and echogenicity can help determine whether the condition is acute or chronic kidney disease. The incidental discovery of a kidney tumour can be highly significant for the patient. Pelvic organ ultrasound in emergency medicine most often focuses on determining bladder fullness and the presence of free fluid in the pelvis. However, it can also aid in diagnosing pregnancy, ectopic pregnancy, determining the cause of bleeding during pregnancy, suspecting ovarian torsion, identifying pyosalpinx, detecting tumours, and more (65).

Ultrasound in Sepsis

Identifying the source of sepsis is crucial for selecting empirical antimicrobial therapy. Ultrasound can strongly suggest sinusitis, pneumonia, endocarditis, pleural empyema, suppurative pericarditis, peritonitis, cholecystitis, cholangitis, pyelonephritis, pyonephrosis,

abscesses in various locations, and more (66). Targeted sampling for microbiological analysis under ultrasound guidance is beneficial. Drainage of purulent collections is essential in managing patients with sepsis and septic shock. Percutaneous aspiration and drainage of empyema and abscesses are minimally invasive and often definitive treatment methods. Even when not definitive, they can contribute to stabilising patients who require surgical intervention.

Interventional Ultrasound

The use of ultrasound to assist in various invasive procedures such as vascular access (central or peripheral), pleural puncture or drainage for effusion or pneumothorax, pericardiocentesis, or drainage of purulent collections in any part of the body is well established (67-70),(68). Ultrasound-guided methods can be categorised as in-plane and out-of-plane. The in-plane technique ensures the needle remains continuously within the ultrasound beam plane during its path to the target lesion.

There is a wide range of additional potential applications of ultrasound in emergency medicine, including musculoskeletal ultrasound for diagnosing fractures, ligament injuries, and muscle injuries, as well as ocular ultrasound, neurological ultrasound, and more.

From our experience, it is better to perform pleural punctures using plastic intravenous cannulas rather than needles prepared for this purpose in puncture kits (71). Usually, it is sufficient to use ultrasound to locate and mark the optimal puncture site, with the procedure carried out without direct ultrasound control. Puncture with a green intravenous cannula does not require local anaesthesia, whereas placing a small drain warrants the use of local anaesthetic. For mechanically ventilated patients who cannot sit upright, a thin drain is preferred, inserted from the side in a semi-recumbent position with the head of the bed elevated. Pericardial puncture is traditionally performed from the epigastrium, which is not straightforward under direct ultrasound guidance. After prior orientation, the puncture is typically performed blindly. When feasible, the preferred approach is pericardiocentesis via the intercostal route, commonly using a high-frequency probe with in-plane technique. This involves placing the probe along the intercostal space to visualise only the thoracic wall and the pericardial fluid layer (72). Ultrasound-guided regional anaesthesia nerve blocks may also be suitable in emergency care (73).

Other Applications

There is a wide range of additional potential applications of ultrasound in emergency medicine, including musculoskeletal ultrasound for diagnosing fractures, ligament injuries, and muscle injuries, as well as ocular ultrasound, neurological ultrasound, and more (74-77). The use of ultrasound in diagnosing and managing paediatric intussusception is one example of replacing conventional radiological and surgical methods with less invasive procedures that avoid ionising radiation, which should be minimised, particularly in children (78). Numerous other examples demonstrate how the use of ultrasound by emergency physicians can be enhanced beyond the basic level. The scope of effective implementation will depend on individual enthusiasm, local conditions, and needs.

Conclusion

Ultrasound is a tool that facilitates and enhances diagnostics in emergency medicine and is increasingly becoming a standard extension of clinical examination. Training in basic ultrasound applications is not demanding. Mastery of one application simplifies the use of ultrasound in others, ultimately leading to proficiency in full-body ultrasound examination. When using ultrasound, it is important to critically assess the reliability of findings and incorporate them into the logic of clinical reasoning. Complementary investigations and specialist consultations enable further verification of findings and improve the acquisition of experience in ultrasound interpretation wherever possible and appropriate.

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ORIGINAL ARTICLE / IZVORNI ZNANSTVENI RAD

INTRODUCTION OF HELICOPTER EMERGENCY MEDICAL SERVICES IN CROATIA: A PERSPECTIVE FROM THE RECEIVING HOSPITAL

UVOĐENJE HITNE HELIKOPTERSKE MEDICINSKE SLUŽBE U HRVATSKOJ: PERSPEKTIVA IZ PRIJEMNE BOLNICE

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Abstract

Background: Helicopter Emergency Medical Services (HEMS) provide rapid transport and advanced medical care for critically ill or injured patients, especially in hard-to-reach areas. In March 2024, HEMS services were introduced in Croatia, with Dubrava University Hospital serving as the primary receiving center for the Zagreb region. This article presents an analysis of the implementation of HEMS in the northwest part of Croatia from the perspective of a receiving hospital.

Methods: A retrospective observational analysis was conducted on patients transported by HEMS to Dubrava University Hospital from March to September 2024. Data on patient demographics, transport times, medical interventions, and outcomes were collected and analyzed.

Results: Out of 41 patients transported by HEMS during the study period, 4 were immediately referred to other specialized centers. The median transport time was 24 minutes. Out of the 37 admitted patients, 14 (38 %) were admitted for surgical management, 16 patients (43 %) were admitted for medical and neurological management, 7 (19 %) were discharged on the same day after workup and observation in the ED.

Conclusion: Introducing HEMS in the Zagreb region has enhanced rapid medical care for critically ill patients, especially polytraumatized patients. Further studies are required to optimize patient flow and improve patient outcomes.

Keywords: helicopter emergency medical services; HEMS; emergency medicine; patient outcomes; resource utilization

Sažetak

Uvod: Hitna helikopterska medicinska služba (HHMS) pruža brzi transport i naprednu medicinsku skrb za kritično bolesne ili ozlijeđene bolesnike, osobito u teško dostupnim područjima. U ožujku 2024. godine, HHMS usluge uvedene su u Hrvatskoj, a Klinička bolnica Dubrava postala je glavni prijemni centar za područje Zagreba. Ovaj članak predstavlja analizu implementacije HHMS-a u sjeverozapadnom dijelu Hrvatske iz perspektive prijemne bolnice.

Metode: Provedena je retrospektivna opservacijska analiza bolesnika prevezenih HHMS-om u Kliničku bolnicu Dubrava od ožujka do rujna 2024. godine. Prikupljeni su podaci o demografiji bolesnika, vremenima transporta, medicinskim intervencijama i ishodima koji su zatim analizirani.

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Rezultati: Od ukupno 41 bolesnika transportiranog helikopterom tijekom razdoblja studije, 4 su odmah upućena drugim specijaliziranim centrima. Medijan vremena transporta bio je 24 minute. Od 37 pregledanih bolesnika, 14 (38 %) bolesnika je bilo hospitalizirano zbog kirurškog liječenja, 16 (43 %) zbog internističkog i neurološkog liječenja, a 7 (19 %) je otpušteno isti dan nakon obrade i promatranja u hitnoj službi.

Zaključak: Uvođenjem HEMS-a u Zagrebu poboljšana je brza medicinska skrb za kritične bolesnike, osobito politraumatizirane. Potrebna su daljnja istraživanja kako bi se optimizirao protok bolesnika i poboljšali ishodi liječenja.

Ključne riječi: Hitna helikopterska medicinska služba; HHMS; hitna medicina: organizacija zdravstvene skrbi

Introduction

Helicopter Emergency Medical Services (HEMS) have become an integral part of modern emergency medicine, providing rapid transport and advanced care for critically ill or injured patients, particularly in regions where ground-based services face limitations. The ability of HEMS to reach remote or hard-to-access locations and deliver on-site advanced interventions has been well documented (1–3). Globally, HEMS have been associated with improved survival rates and better patient outcomes in trauma and other time-sensitive conditions (4,5). However, some studies have questioned the extent of these benefits, reporting no significant difference in mortality when compared to ground emergency medical services (GEMS) (6,7).

In Croatia, emergency medical services have evolved significantly since the 1960s, expanding from urban centers to rural and remote areas (8). The introduction of HEMS was primarily driven by the need to improve response times in challenging terrains, including numerous islands and mountainous regions. Prior to March 2024, HEMS operations were predominantly along the Croatian coast. Recognizing the need for rapid medical interventions inland, HEMS services were extended to the rest of Croatia, with Dubrava University Hospital serving as the primary receiving center for the Zagreb region due to its operational heliport and advanced medical capabilities covering a diverse area of more than 21,000 square kilometers (9,10).

The implementation of HEMS in the Zagreb region aims to address geographical and accessibility challenges, ensuring timely medical interventions for patients requiring urgent transport to tertiary care centers. This includes those with severe trauma, acute cardiac events, neurological emergencies, and other critical conditions where rapid response significantly impacts outcomes (11,12). This study aims to describe patient characteristics, management and outcomes from the receiving hospital's perspective.

Methods Study Design

A retrospective observational analysis was conducted based on hospital information system and medical records from Dubrava University Hospital, including the Prehospital Critical Patient Alert reports (Appendix 1). The study covered the period from April to September 2024, corresponding with the initial six months of HEMS operation in the Zagreb region.

In Croatia, the process of activating Helicopter Emergency Medical Services (HEMS) typically begins when an emergency situation is reported, either through dispatch or by a field doctor on the scene who deems helicopter transport necessary. The activation involves assessing the patient's condition and deciding whether HEMS is the most appropriate solution. Upon arrival at the scene, the medical crew, consisting of a doctor, and a nurse, stabilizes the patient for transport. During the flight, the medical team maintains ongoing care. Dispatch, and when possible, the HEMS team, communicates with the receiving hospital, such as Dubrava University Hospital, through mobile phones or TETRA radios. They provide relevant patient data, which is recorded in the Prehospital Critical Patient Alert (PCPA) by the emergency department triage nurse. The triage nurse activates the opening of the helipad and notifies the appropriate medical teams. Upon landing of the helicopter, the GEMS team receives the patient, who is transferred from the helipad to the emergency department (ED), approximately 300 meters away. Once the patient reaches the hospital, a detailed handover is performed, where the HEMS team or the GEMS team transfers essential patient information to the hospital staff. The hospital then integrates the patient data into the hospital's information system for continuity of care. The ED team performs an initial assessment and manages the patient accordingly. The patient may then undergo diagnostic procedures, receive necessary treatment, or be transferred to the appropriate department for further care. This streamlined process ensures quick, coordinated, and efficient care for critical patients.

Data Collection

Data were collected on all patients transported by HEMS to Dubrava University Hospital during the study period according to the hospital information system and medical records. Variables included patient demographics (age and gender), transport times from dispatch notification to hospital arrival, medical interventions performed

Appendix 1 Prehospital Critical Patient Aler

Date: _____

- Emergency Medical Service

EMS Zagreb EMS County _____ HEMS

- Team 1 Team 2*
- Age _____
- Sex: M F
- Chief complaint/indication for transport
- Mechanism of injury/medical illness
- Significant comorbidities
- Level of consciousness **GCS**_____ **Alert** **Unresponsive**
- Initial vital signs BP _____ mmHg SaO2 _____% pulse _____/min temperature _____°C
- Significant findings in the physical exam
- Administered therapy
- Response to therapy
- Estimated time of arrival _____
- Actual time of arrival _____
- Name of patient, year of birth: _____

Triage nurse: _____

* Team 1 includes a doctor and a nurse, team 2 consists of two medical nurses specialized in emergency medicine

upon arrival (such as surgeries, percutaneous coronary interventions, and thrombolysis), and patient disposition and mortality.

Data Analysis

Descriptive statistics were utilized to summarize the data. Median values were calculated for continuous variables such as age and transport times due to their skewed distribution. Categorical data were presented as frequencies and percentages.

Results

During the study period, we recorded 47 patients that were transported by HEMS to the Dubrava University Hospital. There were six PCPA reports with missing relevant data, meaning the intervention was cancelled or lost to follow up. The study included 41 patients in total, 29 (70 %) male and 12 (30 %) female patients. The age of the patients ranged from 18 to 80 years, with a median age of 63 years. The median transport time from dispatch notification to patient arrival at the hospital was 24 minutes, with transport times ranging between 7 and 59 minutes. The median Expected Time of Arriva (ETA) was 18.5 minutes with ETA ranging between 5 and 92 minutes. Advanced medical interventions were required in 20 patients (49 %). These interventions included immediate surgery, percutaneous coronary interventions, and thrombolysis. Out of the 41 patients, 15 (36 %) were treated surgically, 16 (39 %) were treated and admitted to cardiology and internal medicine, 6 (15 %) had neurological emergencies, and 4 (10 %) were arranged in advance to be immediately transferred to other hospitals for definitive care, i.e. burns center, aortic aneurism center, etc. (Figure 1).

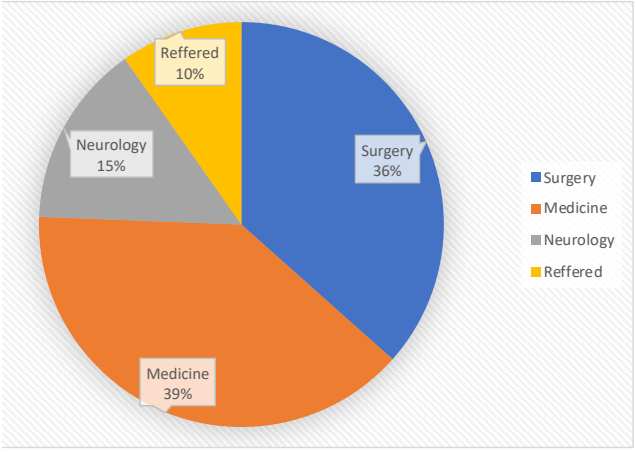

Figure 1. Pie chart showing the distribution of patients by type of emergency

Considering patient disposition, out of the 37 patients, 14 (38 %) were admitted for surgical management, 16 patients (43 %) were admitted for medical management, 7 (19 %) were discharged on the same day after workup and observation in the ED (Figure 2).

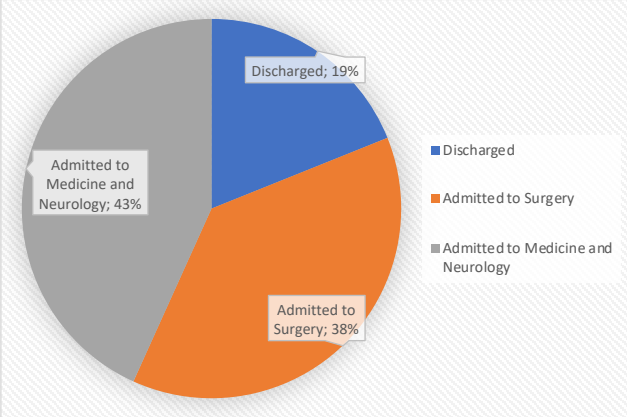

Figure 2. Pie chart presenting patient disposition

There were no recorded deaths in the ED, however two patients (5 %) died during their hospital stay. In the PCPA reports, the most often reported information was the state of consciousness at 18 (44 %) % and estimated time of arrival (ETA) at 32 (76 %).

Discussion

The introduction of HEMS in the Zagreb region has substantially improved the capacity to deliver rapid medical care to critically ill or injured patients. The median transport time of 24 minutes underscores the efficiency of HEMS in overcoming geographical and logistical challenges that may delay GEMS. Rapid response is crucial for conditions where time to treatment is a critical determinant of outcomes, such as acute myocardial infarction, severe trauma, and acute stroke (11,12). The demographic distribution aligns with common patterns observed in emergency medical services, where a higher prevalence of critical conditions is often seen in older adults and males.

> The introduction of HEMS in the Zagreb region enhances the rapid medical care of critically ill patients.

In our study, with a limited sample of interventions, the high proportion of patients requiring advanced medical interventions indicates that HEMS is effectively facilitating access to specialized care for patients in critical need. There was no lethal outcome reported in the emergency department and only 2 (5 %) patients succumbed to injuries within 30 days of admission. While some studies have demonstrated survival benefits associated with HEMS, particularly in severely injured patients (13,14), other research has not found significant differences in mortality when comparing HEMS to GEMS (6,7). A Cochrane review by Galvagno et al. concluded that due to methodological weaknesses and heterogeneity among studies, it is unclear whether HEMS offers a significant advantage over GEMS in terms of mortality outcomes (6).

Our findings are consistent with international studies that highlight both the potential benefits and the complexities associated with HEMS. A Swedish study by Lapidus et al. reported lower mortality rates for trauma patients transported by HEMS despite longer prehospital times, suggesting that the advanced care provided by HEMS personnel offsets time differences (12). Conversely, a study by Beaumont et al. in England found a non-significant survival advantage for patients transported by HEMS and emphasized the challenges in statistically assessing HEMS benefits due to intrinsic patient demographic mismatches (7). Den Hartog et al. demonstrated a survival benefit with physician-staffed HEMS, showing an average of 5.33 additional lives saved per 100 dispatches among severely injured patients (13). However, the cost-effectiveness of HEMS remains a subject of debate. While some studies support the economic viability of HEMS (15), others highlight the need for careful resource allocation due to high operational costs (16).

Effective communication is critical in emergency medical services to ensure optimal patient care. Missing data in the PCPA reports suggests potential for improvement in communication exchange and streamlining patient care. Similar challenges have been reported in other regions, emphasizing the need for standardized communication protocols (17,18). Enhancing communication between HEMS teams, dispatch centers and receiving hospitals is essential to maximize the benefits of HEMS.

Another important observation is time from alerting the receiving hospital of the critically ill patient to the time of arrival. The activation of the hospital emergency response (surgical, medical, anesthesia, radiology, other specialists) for incoming critically ill patients transported via helicopter requires immediate reallocation of resources and personnel to prepare for the patient's arrival. This process often involves staff interrupting ongoing tasks to ensure readiness and availability. However, when the estimated time of arrival (ETA) provided by the helicopter transport team or dispatch center is imprecise or significantly delayed, this creates a critical inefficiency. Prolonged waiting periods, sometimes exceeding 90 minutes, can lead to staff fatigue, distraction, and a decline in preparedness, as focus and team cohesion dissipate over time. Such disruptions not only waste valuable resources but may also negatively impact the team's performance and readiness to provide optimal care upon the patient's arrival (19-23).

Many factors contribute to the HEMS activation itself, which is not the topic of this paper. Nevertheless, there is

always a potential for overutilization of HEMS resources for cases that may not have necessitated air transport. Overutilization of HEMS incurs unnecessary costs and diverts resources from patients who might benefit more significantly from rapid transport. A study from the Central Gulf Coast region in the United States found that 34 % of HEMS transports were potentially unwarranted, resulting in unnecessary healthcare expenditures exceeding 3 million dollars (15). Considering that we are describing a HEMS program at the start of operations, the observation that 19 % of patients were discharged on the same day can be considered part of the learning curve of the teams. According to international studies, activation criteria should focus on specific clinical indicators, severity scores, and geographical considerations (22,23). Standardized criteria can reduce inappropriate HEMS activations and allocate resources to patients who will benefit the most.

Advanced medical interventions were required in 20 patients (49 %), including immediate surgery, percutaneous coronary interventions, and thrombolysis.

Implementing standardized communication procedures between HEMS teams, dispatch centers and receiving hospitals is critical. Dispatchers should provide comprehensive patient information, including vital signs, symptom duration, identification details, and estimated time of arrival. Utilizing technology to share real-time updates securely can further enhance coordination (16,17). Regular training programs for dispatch personnel and medical staff can improve assessment skills, adherence to activation criteria, and communication effectiveness. Training has been shown to enhance the efficiency and effectiveness of emergency medical services (17,25).

Establishing a centralized database to track HEMS interventions and outcomes can facilitate monitoring, evaluation, and continuous improvement. Data-driven approaches enable informed decision-making and policy development (8,26). Comprehensive data collection is essential for conducting cost-benefit analyses and assessing the long-term impact of HEMS.

Limitations

This study is based on observational data from a single center over a limited period. Findings may not be generalizable to other regions or healthcare systems due to differences in infrastructure and population demographics.

Collaborative efforts among policymakers, healthcare providers, and emergency services are crucial to optimize HEMS operations and deliver the best emergency healthcare.

Conclusion

The introduction of HEMS in the Zagreb region represents a significant advancement in Croatia's emergency medical services, enhancing rapid medical care for critically ill patients. Initial observations indicate operational efficiency and effective facilitation of specialized care. There is room for improvement in communication between HEMS, GEMS and the receiving hospital. Future studies with more extensive data and comparative analyses are necessary to evaluate the long-term effectiveness and cost-efficiency of HEMS in Croatia. Collaborative efforts among policymakers, healthcare providers, and emergency services are crucial to optimize HEMS operations and deliver the best emergency healthcare.

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REVIEW ARTICLE / PREGLEDNI ČLANAK

VASOPRESSORS IN TRAUMA PATIENTS: A REVIEW OF INDICATIONS, BENEFITS, AND CONTROVERSIES

VAZOPRESORI U TRAUMATIZIRANIH BOLESNIKA: PREGLED INDIKACIJA, KORISTI I DILEME

*** Višnja Nesek Adam[1,2,3,4], Adis Keranović[4], Anđela Simić[6], Martina Matolić[1], Tamara Murselović[1,2]**

Abstract

Trauma-induced shock, primarily classified as hypovolemic shock, is a critical condition resulting from significant blood loss or fluid shifts, leading to impaired tissue perfusion and oxygenation. The physiological response to this state involves a two-phase process: an initial activation of the sympathetic nervous system (SNS) to maintain perfusion of vital organs, followed by a later phase characterized by receptor downregulation, metabolic acidosis, and the development of multi-organ dysfunction. The use of vasopressors in trauma-induced shock, particularly norepinephrine, is a common approach to managing hypotension. However, their application remains a subject of ongoing debate due to concerns about their potential impact on microcirculatory flow, tissue perfusion, and endothelial function. The choice of vasopressor, optimal dosing, and timing of initiation are contentious issues, as these factors significantly influence patient outcomes. Further research is essential to refine treatment algorithms and improve the prognosis of critically ill trauma patients.

Key words: shock; trauma; vasopressors; multi-organ dysfunction

Sažetak

Traumatski šok, koji se primarno klasificira kao hipovolemijski šok, predstavlja vitalno ugrožavajuće stanje uzrokovano značajnim gubitkom krvi ili pomakom tekućina, što dovodi do smanjene perfuzije i oksigenacije tkiva. Fiziološki odgovor organizma uključuje dvije faze: početnu, koja podrazumijeva aktivaciju simpatičkog živčanog sustava kako bi se održala perfuzija vitalnih organa, te kasniju fazu koja se odlikuje smanjenom osjetljivošću receptora, razvojem metaboličke acidoze i progresivnom disfunkcijom organa. Primjena vazopresora u traumatskom šoku, osobito noradrenalina, postaje sve češći pristup liječenju hipotenzije. Ipak, njihova primjena ostaje predmet rasprava zbog zabrinutosti o njihovom potencijalnom utjecaju na mikrocirkulaciju, perfuziju tkiva i funkciju endotela. Izbor vazopresora, optimalno doziranje i trenutak početka primjene predmet su nesuglasica jer ovi čimbenici značajno utječu na ishod liječenja. Daljnja istraživanja nužna su za razvoj učinkovitih terapijskih algoritama i poboljšanje prognoze kritičnih traumatskih bolesnika.

Ključne riječi: šok; trauma; vazopresori; multiorgansko zatajenje

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Introduction

Trauma-induced hypotension is a leading cause of morbidity and mortality in emergency and critical care settings (1-4). While fluid resuscitation and hemorrhage control are cornerstones of trauma management, the use of vasopressors remains a controversial topic (5). Vasopressors, which include agents such as norepinephrine, epinephrine, vasopressin, dopamine, and phenylephrine, are frequently used in critically ill patients to support blood pressure and organ perfusion. However, their use in trauma patients, especially those in hypovolemic shock, has raised concerns due to their potential to exacerbate tissue ischemia and complicate management.

The debate surrounding vasopressor use in trauma arises from the delicate balance between maintaining perfusion to vital organs and the possible adverse effects of these medications. Vasopressors work by constricting peripheral blood vessels, thereby increasing systemic vascular resistance and improving blood pressure. However, they may reduce blood flow to the microcirculation, impairing oxygen and nutrient delivery to tissues, particularly in already compromised areas. Additionally, excessive vasoconstriction can increase myocardial oxygen demand and contribute to complications such as arrhythmias, organ dysfunction, and even death.

In trauma patients, where rapid resuscitation and hemorrhage control are paramount, the timing and judicious use of vasopressors are critical. While vasopressors can be life-saving, they are not without significant risks, and their role in trauma care is still evolving. This article will explore the pathophysiology of trauma and shock, the rationale for and against vasopressor use in trauma patients, and the current clinical evidence that guides their use in trauma care.

Pathophysiology of Traumatic Shock

Trauma-induced shock is predominantly classified as hypovolemic shock**,** resulting from significant blood loss, fluid shifts, or a combination of both. This loss of effective circulating blood volume leads to a critical reduction in tissue perfusion and oxygenation. In response to trauma, the body initiates a two-phase physiological response to counteract the effects of shock and preserve perfusion to vital organs (6).

In the early stages of trauma-induced shock, the sympathetic nervous system (SNS) is activated as the primary compensatory mechanism to preserve perfusion to vital organs (7). This activation results in the release of catecholamines, including norepinephrine, epinephrine, and dopamine, which exert their effects on adrenergic receptors throughout the cardiovascular system and peripheral tissues to maintain hemodynamic stability.

Hemorrhage precipitates a rapid and pronounced surge in catecholamine levels, particularly epinephrine and norepinephrine, which can increase by 10 to 40 times their normal baseline concentrations (8). These catecholamines act on β-adrenergic receptors to increase heart rate (chronotropy) and myocardial contractility (inotropy), thereby enhancing cardiac output. Simultaneously, they engage α-adrenergic receptors to induce peripheral vasoconstriction, redirecting blood flow to critical organs such as the brain and heart while maintaining systemic vascular resistance and blood pressure. This neurohumoral response ensures the temporary stabilization of vital physiological functions during the acute phase of hypovolemic shock, buying crucial time for interventions to address the underlying cause of blood loss.

One of the primary responses to trauma is tachycardia, where the heart rate increases to compensate for the decreased stroke volume and circulating blood volume. This helps to maintain cardiac output and support organ perfusion. At the same time, the SNS triggers widespread vasoconstriction through the release of norepinephrine and epinephrine, which act on alpha-adrenergic receptors in vascular smooth muscle. This causes an increase in systemic vascular resistance (SVR) and elevates blood pressure, helping to direct blood flow to critical organs such as the brain, heart, and kidneys. In parallel, blood is preferentially shunted away from less vital organs, including the gastrointestinal tract, skin, and muscles, in an effort to preserve perfusion to the organs most vital for survival.

Additionally, the activation of the renin-angiotensin-aldosterone system (RAAS) plays a crucial role in the body's compensatory response. The drop in blood pressure triggered by the loss of blood volume stimulates the kidneys to release renin, which leads to the production of angiotensin II. Angiotensin II acts as a potent vasoconstrictor, further increasing SVR and supporting blood pressure. It also stimulates the release of aldosterone, which promotes sodium and water retention, attempting to restore circulating volume and prevent further hypotension. Together, these mechanisms work to mitigate the effects of hypovolemic shock and sustain critical physiological functions (fig. 1).

While these compensatory mechanisms initially help maintain blood flow to vital organs, their effectiveness decreases over time, especially in severe trauma. Prolonged activation of the sympathetic nervous system leads to a downregulation of catecholamine receptors**,** particularly beta-adrenergic receptors. This reduces receptor sensitivity, making the body less responsive to catecholamines. Despite continued release of these hormones, it becomes increasingly difficult to maintain blood pressure and tissue perfusion, signaling the progression to the second phase of shock.

In addition, prolonged vasoconstriction can cause end-organ ischemia, limiting oxygen delivery to tissues. Due to end-organ ischemia and impaired oxygen delivery, anaerobic metabolism ensues leading to metabolic

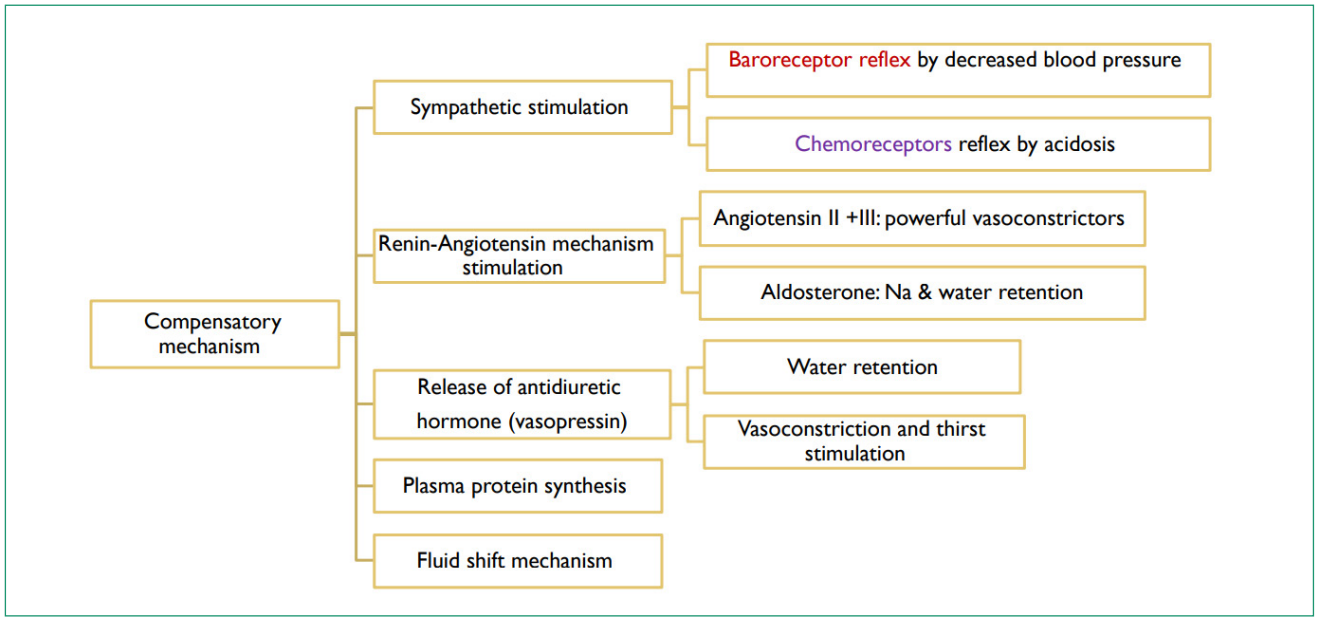

Figure 1. Compensatory mechanisms of haemorrhagic shock

acidosis (9). The acidosis further worsens the situation by inactivating and reducing the number of vasopressor receptors, weakening the body's ability to stabilize circulation. These changes highlight the importance of timely treatment to prevent shock from advancing and causing permanent organ damage.

Trauma-induced hypotension is a major cause of morbidity and mortality in emergency and critical care, with vasopressors used to support blood pressure but remaining controversial in trauma management.

As the trauma progresses, the body enters a depressive phase, marked by the failure of compensatory mechanisms and the onset of organ dysfunction. The ongoing hemorrhage, coupled with the inflammatory response to trauma, depletes the body's ability to sustain sympathetic activation. This results in the loss of vasoconstriction and a decline in blood pressure, further compromising perfusion to tissues and organs. Endothelial dysfunction, triggered by inflammatory mediators, leads to microvascular injury, causing vasodilation and increased capillary permeability (10). This further exacerbates the loss of blood volume and impairs the ability of the microcirculation to deliver oxygen and nutrients to tissues, worsening tissue hypoxia and metabolic acidosis. Metabolic acidosis results from anaerobic metabolism, which occurs when oxygen supply to tissues is insufficient. The accumulation of lactic acid contributes to a decrease in pH, further impairing cellular function and exacerbating shock. Additionally, the inflammatory response, along with endothelial damage, contributes to coagulopathy, which impairs the blood's ability to clot and prolongs hemorrhage. The combination of prolonged blood loss and coagulopathy worsens the hypovolemia, increasing the severity of shock and leading to multi-organ dysfunction. In this depressive phase, the body's compensatory mechanisms are overwhelmed, and vital organ perfusion may deteriorate despite ongoing efforts to restore blood volume and pressure. Multi-organ dysfunction becomes more likely, and survival becomes increasingly dependent on effective and timely interventions. These interventions include fluid resuscitation to restore blood volume, hemorrhage control to stop the source of bleeding, and in some cases the careful use of vasopressors such as norepinephrine or vassopresin to maintain blood pressure and support organ perfusion. Vasopressors can help to stabilize hemodynamics and improve tissue perfusion when the body's own compensatory mechanisms are no longer sufficient support perfusion and stabilize blood pressure.

Understanding the two-phase response in trauma-induced shock - beginning with sympathetic activation and catecholamine release, followed by receptor downregulation and failure of compensatory mechanisms - is critical for guiding therapeutic interventions. The proper management of trauma-induced shock requires timely interventions to address both the early compensatory phase and the later depressive phase, with the goal of improving tissue perfusion and preventing organ failure.

Shock-Induced Endotheliopathy

As already emphasized, a significant factor contributing to poor outcomes in trauma patients is endothelial injury and dysfunction. In hemorrhagic shock, the endothelium is subjected to inflammatory mediators, shear stress, and

ischemia-reperfusion injury, all of which contribute to a condition known as shock-induced endotheliopathy (SHINE) (11,12). SHINE is a critical factor in the pathophysiology of post-traumatic hemorrhagic shock and plays a key role in the progression of shock-related complications. The endothelium is crucial for maintaining vascular homeostasis, with functions that include preserving vascular patency, regulating fluid permeability, and controlling vasomotor tone. Furthermore, the endothelium contributes to natural anticoagulation and the maintenance of vascular integrity through its glycocalyx, a protective layer made of glycoproteins and proteoglycans that houses important anticoagulant molecules like heparinoids and antithrombin.

In the context of SHINE, endothelial dysfunction occurs as a result of glycocalyx degradation, increased vascular permeability, and impaired anticoagulant properties. This dysfunction leads to microvascular thrombosis, edema, and tissue hypoxia. The damage to the glycocalyx is particularly harmful as it disrupts the normal endothelial barrier function, increasing the likelihood of clot formation and exacerbating inflammation. These changes contribute to a vicious cycle of further endothelial damage, impaired circulation, and compromised organ function, which worsens the overall severity of hemorrhagic shock.

The cumulative effects of endothelial dysfunction worsen the progression of shock, contributing to multi-organ failure and poor clinical outcomes. Addressing endotheliopathy is crucial for improving survival and recovery in hemorrhagic shock. Emerging therapies aim to preserve the glycocalyx and restore endothelial function. These strategies include fluid resuscitation with balanced crystalloids, antioxidants, and glycoprotein stabilizers, which help protect the endothelium from further damage. These approaches enhance the natural protective and anticoagulant properties of the endothelium, representing promising interventions to mitigate shock-induced endotheliopathy (SHINE) and improve clinical outcomes.

Indications for Vasopressors in Trauma (Why Not):

As we mention before, the use of vasopressors in trauma-induced hypotension, particularly in cases of hypovolemic shock, has long been a subject of debate in critical care. While vasopressors are indispensable in certain clinical scenarios such as septic or cardiogenic shock, their application in trauma presents unique challenges. The underlying pathophysiology of trauma-induced shock - characterized primarily by significant blood loss and hypovolemia - raises critical concerns about the efficacy and safety of vasopressors. Literature consistently emphasizes the need for caution regarding the routine use of vasopressors in trauma, highlighting the significant risks they pose to patients already in a fragile physiological condition (7,13,14).

Trauma-induced shock involves an initial compensatory phase with sympathetic activation, followed by a depressive phase with receptor downregulation and organ dysfunction. Timely interventions, like fluid resuscitation and vasopressors, are key to improving outcomes.

Vasopressors act by increasing systemic vascular resistance through vasoconstriction, which can lead to reduced perfusion in the microcirculation. In trauma-induced hypovolemia, the primary issue is the lack of circulating blood volume, not vascular tone (15). By further constricting blood vessels, vasopressors can worsen tissue ischemia and hypoxia, particularly in already compromised areas. This effect increases the risk of organ dysfunction and delayed recovery, as oxygen and nutrient delivery to tissues becomes insufficient.

In addition to their impact on tissue perfusion, vasopressors can aggravate the endothelial dysfunction inherent to trauma-induced shock. Vasopressors can intensify endothelial dysfunction by increasing shear stress, increased vascular permeability, and impaired anticoagulant properties of the endothelium (16). This worsens microvascular injury and contributes to the inflammatory cascade, leading to further complications such as edema, coagulopathy, and impaired oxygenation.

Another significant concern is the effect of vasopressors on myocardial oxygen demand. Vasopressors such as norepinephrine and epinephrine stimulate alpha- and beta-adrenergic receptors, increasing vascular resistance and heart rate. While this temporarily raises blood pressure, it also significantly increases myocardial oxygen demand. In the context of trauma, where the heart is already compensating for reduced preload and systemic hypoperfusion, this additional workload can precipitate cardiac dysfunction, arrhythmias, and myocardial ischemia.

A critical concern with the use of vasopressors in trauma management is their potential to mask the underlying hypovolemia (13,17). By artificially augmenting systemic arterial pressure, vasopressors can create a deceptive appearance of hemodynamic stability. This apparent normalization of blood pressure risks delaying definitive interventions, such as aggressive fluid resuscitation and rapid hemorrhage control, which are essential for correcting the primary cause of hypotension. Such delays may exacerbate the progression of shock and significantly compromise patient outcomes, as effective trauma care hinges on timely volume restoration and hemorrhage cessation to stabilize perfusion and prevent multi-organ failure.

In severe trauma, the prolonged release of endogenous catecholamines can lead to desensitization of adrenergic

receptors (18). This downregulation diminishes the efficacy of both endogenous and exogenous vasopressors. As a result, reliance on these medications during the later stages of shock may produce diminishing returns, failing to effectively stabilize hemodynamics and potentially introducing additional risks, including worsened tissue perfusion.

Some study emphasizes that early vasopressor infusion in trauma patients increased the mortality rate, regardless of trauma severity (19,20). The underlying causes included low arterial pressure, higher fluid requirements, and elevated serum creatinine levels. These findings highlight the risks associated with the premature use of vasopressors in trauma patients, particularly when volume resuscitation and hemorrhage control have not been adequately addressed.

In conclusion, it is important to emphasize that the literature provides limited support for the routine use of vasopressors in trauma-induced hypovolemic shock. Current guidelines prioritize fluid resuscitation, blood product administration, and hemorrhage control as first-line therapies. Vasopressors are typically reserved for refractory cases where hypotension persists despite these interventions, and even then, their use must be carefully evaluated against the potential risks and complications. Use of vasopressors is not recommended according to the Advanced Trauma Life Support management principles (21).

Indications for Vasopressors in Trauma (Why Yes):

Despite studies linking vasopressor use to increased mortality in trauma patients (19,20), there are compelling reasons why vasopressors are increasingly being discussed and utilized in modern trauma management. One of the key factors contributing to this shift is the growing recognition of the complexities of trauma-induced shock, particularly hemorrhagic shock, and the limitations of traditional fluid resuscitation. Hemorrhagic shock, in particular, can be difficult to manage with volume resuscitation alone, especially in cases where blood loss is substantial, and organ perfusion cannot be adequately restored.

While early vasopressor use has been associated with higher mortality due to their potential to mask the underlying cause of hypovolemia and worsen ischemia, more recent literature suggests that in certain situations, low-dose vasopressors may be beneficial, particularly when initial fluid resuscitation fails to maintain adequate blood pressure and organ perfusion (7,22). A retrospective study highlighted that, in some cases, low-dose norepinephrine helped stabilize trauma patients and prevent progression to refractory shock, where conventional treatments may have failed (23). This evolving perspective reflects an increasing understanding that the management of trauma-induced shock is multifaceted and not solely reliant on volume resuscitation.

Moreover, the second phase of hemorrhagic shock, after bleeding has been controlled, can lead to a sepsis-like response triggered by ischemia/reperfusion (I/R) injury, which includes oxidative stress, and the systemic release of cytokines. These processes can significantly impair vascular tone and further compromise organ perfusion. Additionally, the administration of analgesic and sedative medications, which are essential for managing pain and agitation in hemorrhagic shock patients, can further compromise the vasoconstrictor response, exacerbating the effects of shock. These factors contribute to persistent hypotension and inadequate tissue perfusion, underlining the need for vasopressors to stabilize blood pressure, restore tissue perfusion, and prevent further complications in the critical phase of recovery (24).

Low-dose vasopressors, such as norepinephrine, are increasingly being used as adjuncts to volume resuscitation to stabilize blood pressure, improve tissue perfusion, and prevent multi-organ failure. These agents are typically reserved for cases where hypotension persists despite adequate fluid replacement and hemorrhage control. Research has demonstrated that, when carefully titrated, vasopressors can be a potentially lifesaving option in trauma care. A study by Zhang et al. (25) found that early use of norepinephrine improved survival rates in patients with traumatic hemorrhagic shock by helping to maintain adequate perfusion during the critical early stages of recovery.

Furthermore, the use of vasopressors in trauma care reflects an evolving understanding of the need for individualized treatment. While there are significant risks, such as exacerbating ischemia or delaying the recognition of hemorrhage, the careful titration of vasopressors offers a nuanced approach that can balance the need for blood pressure support with the potential for harm. A study by Gupta et al. (7) suggested that vasopressors may be particularly beneficial in trauma patients who experience ongoing hypotension despite sufficient fluid resuscitation, helping to prevent the transition to irreversible shock. This growing trend highlights the limitations of relying solely on fluids and blood products in severe traumatic shock. Vasopressors now play a key role in managing complex, life-threatening conditions, where simply addressing volume loss through resuscitation may not be sufficient.

This shift toward considering vasopressors as part of a broader, more personalized treatment strategy is also reflected in recent clinical guidelines, which recommend their use for cases of shock unresponsive to volume resuscitation (26). In conclusion, while the role of vasopressors in trauma management continues to evolve, their careful use in selected patients can offer significant benefits by maintaining vital organ perfusion and preventing further deterioration. As our understanding of trauma-induced shock deepens, the integration of vasopressors into treatment strategies will likely become more refined, ultimately improving patient outcomes during this critical phase of care.

More question than answer: which, when, and how much vasopressor?

The choice of vasopressor in trauma also remains a subject of ongoing debate. While current guidelines recommend norepinephrine as the first-line vasopressor for managing shock due to its well-established efficacy in improving blood pressure and organ perfusion, there is increasing interest in the potential role of vasopressin. Vasopressin, a potent vasoconstrictor with a different mechanism of action, has gained attention for its ability to enhance vascular tone without the negative effects on cardiac output seen with norepinephrine. Some studies suggest that vasopressin may be beneficial in certain traumatic shock cases.

Vasopressors should be used with caution in trauma-induced hypovolemic shock as they can worsen tissue ischemia, endothelial dysfunction, and delay necessary interventions like fluid resuscitation and hemorrhage control.

One of the most significant advantages of vasopressin in trauma patients is its ability to retain its pressor effects during severe acidosis and hypoxemia, conditions that often accompany traumatic shock (27). Unlike norepinephrine, whose vasoconstrictive properties may be diminished under these circumstances, vasopressin continues to function effectively in these critical conditions. This makes vasopressin particularly useful in refractory circulatory shock**,** where conventional vasopressors like norepinephrine may fail to restore adequate blood pressure and organ perfusion. Another notable benefit of vasopressin is its ability to inhibit nitric oxide (NO) synthesis, which plays a crucial role in maintaining vascular tone. In shock states, excessive NO production can exacerbate vasodilation, worsening hypotension and compromising tissue perfusion. By inhibiting NO synthesis, vasopressin counteracts the vasodilatory effects of NO, thereby helping to stabilize vascular tone and blood pressure (28). This action is particularly advantageous in trauma patients where excessive vasodilation can be a significant contributor to shock.

Additionally, vasopressin improves renal perfusion, which is essential in preventing acute kidney injury, a common complication in patients with severe trauma and shock. Vasopressin achieves this by causing vasodilation of the efferent renal arterioles, which contrasts with the vasoconstrictive properties of catecholamines such as norepinephrine**.** This mechanism helps maintain renal blood flow and glomerular filtration, reducing the risk of renal failure, which is often seen in critically ill patients requiring intensive resuscitation (29).

In contrast to norepinephrine, which can cause significant pulmonary vasoconstriction, vasopressin has a milder effect on the lungs (30). In fact, vasopressin can promote pulmonary vasodilation, which is particularly beneficial in trauma patients with respiratory compromise. This effect reduces the workload on the heart and improves oxygenation without exacerbating pulmonary hypertension, a common complication associated with high-dose catecholamine therapy.

Vasopressin also offers a significant advantage in terms of cardiac safety. High doses of norepinephrine are often associated with an increased incidence of arrhythmias**,** which can worsen outcomes in trauma patients with pre-existing cardiac instability. Vasopressin, on the other hand, has been shown to cause fewer arrhythmias compared to norepinephrine, making it a safer option for patients at risk for cardiac complications. This is particularly important in patients with traumatic injuries that may already stress the cardiovascular system, as minimizing arrhythmias can improve overall prognosis.

One of the unique features of vasopressin is its action as an indirect vasoconstrictor. It enhances the sensitivity of smooth muscle cells to circulating catecholamines, such as norepinephrine, which improves the efficacy of these agents at lower doses (31). This mechanism can reduce the need for high-dose norepinephrine or other catecholamines, minimizing the risk of adverse effects such as arrhythmias or excessive vasoconstriction, which can compromise organ perfusion.

Vasopressors can be useful in trauma management, particularly when fluid resuscitation alone fails to restore blood pressure and organ perfusion, helping to stabilize the patient and prevent further complications.

Moreover, vasopressin has immunomodulatory effects that can help mitigate the inflammatory response often triggered by trauma and shock (32). The inflammatory response in trauma patients can lead to widespread tissue damage, organ failure, and sepsis. By modulating the immune system, vasopressin may help reduce these harmful effects, promoting better recovery and reducing the incidence of secondary complications like infection.

In conclusion, vasopressin offers several distinct advantages over norepinephrine in the management of trauma-induced shock. Its ability to function in hypoxic and acidotic conditions, its effects on renal and splanchnic perfusion, and its relatively lower risk of arrhythmias make it a valuable adjunct to traditional vasopressors. While it should not replace norepinephrine as the first-line therapy in all cases, vasopressin has become an increasingly important tool in the management of refractory shock, offering a more targeted approach to treatment. As our understanding of trauma and shock physiology continues to evolve, vasopressin is likely to play an even greater role in modern trauma care, providing a safer and more effective option for critically ill patients.

Conclusion

The management of trauma-induced shock remains complex, with ongoing debates surrounding the use of vasopressors. Norepinephrine has long been the first-line treatment for shock, but increasing interest in vasopressin reflects a growing recognition of its potential benefits, particularly in severe, refractory cases. Vasopressin's ability to maintain vascular tone in hypoxic and acidotic environments, its positive effects on renal and splanchnic perfusion, and its lower risk of arrhythmias offer several advantages over norepinephrine. However, its use must be carefully evaluated, as improper or premature administration of vasopressors can worsen ischemia and delay vital interventions. Ultimately, trauma care requires a personalized approach, and vasopressors should be employed based on the individual patient's response to initial interventions, with fluid resuscitation and hemorrhage control as the primary strategies. As our understanding of trauma and shock physiology advances, vasopressin may play an increasingly pivotal role in optimizing outcomes for critically ill trauma patients.

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PREGLEDNI ČLANAK / REVIEW ARTICLE

PRIMJENA ADRENALINA TIJEKOM KARDIOPULMONALNE REANIMACIJE ODRASLIH: DVOSJEKLI MAČ?

ADRENALINE USE DURING ADULT CARDIOPULMONARY RESUSCITATION: A DOUBLE-EDGED SWORD?

Ingrid Bošan-Kilibarda[1], Višnja Nesek Adam[2,3,4,5]

Sažetak

Adrenalin je već dugi niz godina ključna komponenta smjernica za napredno održavanje života kod bolesnika sa srčanim zastojem. Unatoč njegovoj širokoj primjeni u kardiopulmonalnoj reanimaciji (KPR), njegova učinkovitost i sigurnost i dalje su predmet rasprava. Iako adrenalin povećava šanse za povratak spontane cirkulacije i preživljavanje do prijema i otpusta iz bolnice, učinci na dugoročno preživljavanje i neurološke ishode nisu jasni.

Tijekom godina istraživači i kliničari postavljali su pitanje optimalne doze adrenalina jer standardna doza, 1 mg po primjeni kod odrasli, nije prilagođena tjelesnoj težini. Povijesno gledano, standardna doza od 1 mg adrenalina koristila se u kirurškim salama za intrakardijalne injekcije. Ustanovilo se kako više doze adrenalina ne pružaju bolje ishode i mogu biti potencijalno štetne. Optimalno vrijeme i interval primjene adrenalina tijekom KPR nije poznat, iako provedene studija ukazuju kako rana primjena adrenalina i kraći intervali između doza mogu poboljšati postotak povratka spontane cirkulacije i preživljavanje, iako možda neće rezultirati značajno boljim neurološkim ishodima.

Ovaj članak nudi pregled postojećih istraživanja koja se bave pitanjima u vezi s primjenom adrenalina tijekom KPR-a. Varijabilnost rezultata podupire potrebu za provedbom multicentričnih, prospektivnih randomiziranih studija koje bi istražile optimalnu dozu adrenalina, ukupan broj doza iznad kojih nema dodatne koristi, kao i optimalne intervale između doza. Također, potrebno je razmotriti alternative postojećim protokolima. Buduća istraživanja trebaju se usmjeriti na dugoročne ishode, koji nadilaze povratak spontane cirkulacije kako bi se poboljšali funkcionalni rezultati za pacijente sa srčanim zastojem.

Ključne riječi: adrenalin; kardipulmonalna reanimacija odraslih; prijepori

Abstract

For many years, adrenaline has been a key component of advanced life support guidelines for patients experiencing cardiac arrest. Despite its prolonged use during cardiopulmonary resuscitation (CPR), its efficacy and safety remain subjects of debate. Adrenaline increases the chances of return of spontaneous circulation and survival to hospital admission and discharge, but its effects on long-term survival and neurological outcomes are ambiguous. Over time, clinicians and researchers have questioned the optimal dose of adrenaline, as the standard adult dose of 1 mg per administration is not adjusted for body weight. Historically, this dose was used for intracardiac injections in surgical settings. Further studies have indicated

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that higher doses of adrenaline do not lead to better outcomes and may even be potentially harmful. The optimal timing and interval for administering adrenaline during CPR remain unclear, though some studies suggest that early administration and shorter intervals between doses may improve ROSC and survival rates, although these factors may not result in significantly better neurological outcomes. This article provides a brief overview of the literature and research results concerning key issues related to the use of adrenaline during CPR. The variability of results strongly supports the need for multicenter, prospective randomized studies to determine the optimal dose, the total number of doses beyond which no further benefit is gained, and the ideal timing and intervals between doses. Additionally, alternatives to current protocols should be explored. Future research should focus on long-term outcomes that extend beyond ROSC in order to achieve better functional outcomes for patients with cardiac arrest.

Keywords: adrenaline; cardiopulmonary resuscitation; adult; controversies

Uvod

Adrenalin je već dugi niz godina ključna komponenta smjernica za napredno održavanje života (engl. *Advance life support, ALS*) u liječenju bolesnika sa srčanim zastojem. Kao kateholamin, adrenalin djeluje stimulirajući alfa i beta adrenergičke receptore. Učincii na β-adrenergičke receptore su izraženiji pri nižim dozama, dok se α-adrenergički učinci javljaju pri višim dozama (1). Stimulacija alfa-1 receptora u glatkim mišićima krvnih žila uzrokuje vazokonstrikciju (bez konstrikcije koronarnih i cerebralnih krvnih žila) i povećanja sistemskog perifernog otpora što uzrokuje povećanje sistoličkog i dijastoličkog tlaka tijekom masaže srca. Povećanje dijastoličkog tlaka u aorti, zauzvrat, poboljšava tlak koronarne perfuzije (engl. *coronary perfusion pressure, CPP*) i tlak cerebralne perfuzije (engl. *cerebral erfusion pressure, CePP*). Ključni čimbenik za povratak spontane cirkulacije (*engl.* return of spontaneous circulation, ROSC) je postizanje odgovarajućeg gradijenta između dijastoličkog tlaka u aorti i tlaka u desnoj pretklijetki. Što je veća razlika tlakova, to je bolja koronarna perfuzija (2-4). Optimalna vrijednost perfuzijskog tlaka srca iznosi ≥15-20 mmHg, budući da se kod nižih vrijednosti tlaka rijetko postiže ROSC (5).

Adrenalin je ključan u naprednoj kardiopulmonalnoj reanimaciji jer povećava sistemski tlak i koronarnu perfuziju, što poboljšava šanse za povratak spontane cirkulacije. Ipak, postoje zabrinutosti zbog njegovog utjecaja na mikrocirkulaciju i neurološke ishode, što zahtijeva daljnja istraživanja za optimizaciju primjene

Iako adrenalin povećava globalni protok krvi u mozgu i koronarnim arterijama, može smanjiti mikrocirkulacijski protok što predstavlja izazov za optimizaciju cerebralne perfuzije. Također, nakon što je postignut ROSC, pretjerano visoke koncentracije adrenalina u plazmi mogu uzrokovati tahikardiju (što povećava potrebu za kisikom) i aritmije, uključujući ventrikulsku tahikardiju (VT) i ventrikulsku fibrilaciju (VF) što može pogoršati klinički ishod (2,6). Kombinacija vazokonstrikcije i njegov inotropni učinak čine adrenalin iznimno korisnim lijekom u povećanju učinkovitosti KPR-a, osobito u slučaju asistolije i električne aktivnosti bez pulsa (7).

Povijest adrenalina u znanosti o KPR

Adrenalin su početkom 20. stoljeća neovisno izolirali Takamine i Abel, čime je započela era istraživanja KPR usmjerena na razumijevanje i poboljšanje hemodinamskih čimbenika u stanju šoka i srčanog zastoja (8).

Prvu dokumentiranu primjenu adrenalina u kardiopulmonalnoj reanimaciji opisali su Crile i Dolley 1906. godine, tijekom eksperimenata na psima. U svojim istraživanjima, inducirali su srčani zastoj gušenjem kod pasa, a zatim su primjenjivali otvorenu srčanu masažu zajedno s intravenskom, intraarterijskom ili intrakardijalnom primjenom adrenalina. Izvijestili su da su psi koji su primili 1-2 mg adrenalina uz "srčanu masažu, umjetnu ventilaciju i infuziju fiziološke otopine intravenski" imali veće šanse za povratak spontane cirkulacije i normalno disanje, no nisu povratili svijest.

Posebno kada su korištene veće doze adrenalina. Istraživanje je također pokazalo da je uspješna KPR bila moguća samo ako je tijekom postupka postignuta vrijednost dijastoličkog tlaka u aorti između 30 i 40 mmHg. Na neki način, ovo otkriće bilo je ispred svog vremena, budući da današnji dokazi ukazuju na to da adrenalin poboljšava učestalost ROSC-a nakon srčanog zastoja, ali ne utječe na neurološke ili

dugoročne ishode (9). Nažalost, ovi su eksperimenti, koji su nesumnjivo postavili temelje moderne KPR, bili zanemareni sve do sredine 20. stoljeća.

Ponovno otkriće vanjske masaže srca, pola stoljeća kasnije, zajedno s razvojem defibrilacije, dovelo je do ponovne potvrde adrenalina kao ključnog lijeka u KPR-u (10). S razvojem ranih smjernica za kardiopulmonalnu reanimaciju tijekom 1960-ih godina, adrenalin je prvi put uključen u postupnike. Pearson i Redding 1963. godine ponovili su eksperimente Crila i Dolleya na psima te su zaključili da ponovljena primjena 1 mg adrenalina intrakardijalno, nakon izazvanog srčanog zastoja uslijed asfiksije, uz srčanu masažu, mehaničku ventilaciju i defibrilaciju, poboljšava preživljavanje. ROSC je postignut u 9 od 10 pasa, dok je u skupini bez adrenalina ROSC postignut samo u 1 od 10 pasa.

Također, potvrdili su da postoji korelacija između umjetno izazvanog dijastoličkog tlaka u aorti i uspjeha KPR te da je „prag preživljavanja" dijastolički tlak od 40 mmHg. Nadalje, potvrđeni su Crilovi nalazi da sama masaža srca bez primjene adrenalina vrlo rijetko može postići potreban dijastolički tlak. Ova opažanja, zajedno s anegdotalnim kliničkim iskustvima opisanima u istom radu, navela su Pearsona i Reddinga da zaključe kako je „adrenalin od velike koristi u vraćanju spontane cirkulacije" (11).

Istraživanja Pearsona i Reddinga pojavila su se u ključnom trenutku za razvoj znanosti o kardiopulmonalnoj reanimaciji. Njihovo uspješno ponavljanje eksperimenata Crilea i Dolleyja značajno je pridonijelo uvođenju adrenalina kao temeljnog farmakološkog sredstva u KPR, a njihovi eksperimentalni nalazi bili su dovoljni da se adrenalin preporuči kao lijek izbora u prvim dokumentiranim smjernicama za primjenu adrenalina, koje je 1974. godine usvojilo Američko kardiološko društvo. Povijesno gledano, standardna doza od 1 mg adrenalina korištena je u kirurškim salama za intrakardijalne injekcije, jer su kirurzi primijetili da doze od 1 do 3 mg adrenalina učinkovito pokreću srce nakon zastoja. Kada su 1970-ih godina prvi put izrađene smjernice za KPR, pretpostavljalo se da će 1 mg intravenskog adrenalina imati sličan učinak kao i intrakardijalna injekcija iste doze (12). Tako je doza od 1 mg adrenalina, koju su Crile i Dolley odabrali prije više od stoljeća, postala standard za kardiopulmonalnu reanimaciju odraslih bolesnika i ostala je na snazi do danas.

Unatoč širokoj primjeni adrenalina u kardiopulmonalnoj reanimaciji i dalje postoje neodgovorena pitanja o njegovom utjecaju na dugoročne neurološke ishode i optimalnoj dozi.

Smjernice Europskog vijeća za reanimatologiju (engl. *European Resuscitation Council, ERC*) iz 2021. godine preporučuju primjenu adrenalina u dozi od 1 mg svakih 3 do 5 minuta, intravenskim (iv.) ili intraosealnim (io.) pristupom, u kardiopulmonalnoj reanimaciji (KPR) odraslih bolesnika koji dožive srčani zastoj. U slučajevima srčanog zastoja s ritmom koji se ne defibrilira, adrenalin od 1 mg treba primijeniti što je prije moguće iv./io. U slučaju srčanog zastoja s ritmom koji se defibrilira adrenalin od 1 mg primjenjuje se iv./io nakon treće defibrilacije (13).

Unatoč širokoj primjeni adrenalina, još uvijek postoje brojna pitanja na koja je potrebno odgovoriti. U dokumentu Međunarodnog konsenzusa o znanosti KPR i hitne kardiovaskularne skrbi s preporukama za liječenje liječenje (engl. *Cardiovascular Care Science With Treatment Recommendations CoSTR*) identificirane su praznine u dostupnim podacima vezane za primjenu adrenalina tijekom KPR kao što su: utjecaj adrenalina na povoljan ili nepovoljan neurološki ishod, optimalna doza adrenalina za pojedine bolesnike, optimalno vrijeme primjene adrenalina u odnosu na defibrilaciju, optimalni interval doziranja adrenalina, nedostatak evaluacije primjene adrenalina kod srčanog zastoja u bolnici (14).

Učinkovitost adrenalina u postizanju ROSC-a, učinak na dugoročno preživljavanje i neurološki ishodi

Jacobs i sur. proveli su randomizirano dvostruko slijepo ispitivanje kontrolirano placebom u kojem su usporedili primjenu adrenalina s placebom u slučajevima izvanbolničkog srčanog zastoja. Rezultati su pokazali kako je primjena adrenalina značajno povećala učestalost ROSC-a u usporedbi s placebom kao i udio bolesnika primljenih u bolnicu. Međutim, dugoročno preživljavanje do otpusta iz bolnice nije doseglo statističku značajnost (15). Meta-analiza koja je obuhvatila 19 studija, potvrdila je veću učinkovitost adrenalina u postizanju ROSC-a i preživljavanju do otpusta iz bolnice, posebno kod ritmova koji se ne defibriliraju (16). Rezultati zabilježeni u istraživanju Hagihare i sur. pokazali su kako bolesnici, njih približno 15.000, u kojih je primjenjivan adrenalin tijekom izvanbolničke KPR imaju značajno veću vjerojatnost ROSC-a prije dolaska u bolnicu u usporedbi s većinom ostalih bolesnika u kojih nije primijenjen adrenalin tijekom KPR-a. Međutim, ista skupina bolesnika imala je značajno lošiji jednomjesečni ishod: preživljenje je bilo dvostruko niže, a preživljenje s dobrim ili blago oštećenim moždanim funkcijama bilo je trostruko niže (17). Unatoč povećanju ROSC-a, dugoročno preživljavanje i neurološki ishodi preživjelih nakon srčanog zastoja često su nepovoljni. U istraživanju Olasveengena i suradnika, proučavajući dugoročno preživljavanje, pokazano je da primjena adrenalina povećava učestalost kratkoročnog preživljavanja, no nije donijela statistički značajno poboljšanje preživljavanja do otpusta iz bolnice ili dugoročnog preživljavanja (18).

PARAMEDIC-2 studija, najveća randomizirana dvostruko slijepa prospektivna studija koja je obuhvatila

8014 bolesnika, utvrdila je značajno veću učestalost preživljavanja nakon 30 dana kod bolesnika koji su primili adrenalin u odnosu na placebo. Međutim, neurološki ishodi nisu bili povoljniji, a među preživjelima koji su primili adrenalin zabilježena je veća učestalost nepovoljnih neuroloških ishoda (19).

Ove rezultate važno je razmotriti u kontekstu specifičnih ograničenja, jer je u PARAMEDIC-2 studiji čak 37 % slučajeva srčanog zastoja nastalo bez prisutnih svjedoka, a prosječno vrijeme do primjene adrenalina bilo je 21 minuta, što može značajno utjecati na lošije neurološke ishode, osobito u slučajevima bez prisutnosti svjedoka. To ukazuje na ključnu ulogu vremena intervencije, kao i drugih čimbenika koji mogu utjecati na uspjeh terapije adrenalinom (20). Dugoročno praćenje PARAMEDIC-2 studije također nije pokazalo značajna poboljšanja u povoljnim neurološkim ishodima, unatoč većem preživljavanja tijekom 12-mjesečnog praćenja (21). Meta-analiza Ludwina i suradnika dodatno je ukazala na ograničenja adrenalina u dugoročnom preživljavanju. Iako su ROSC i preživljavanje do otpusta iz bolnice bili veći, povoljni neurološki ishodi nisu pokazali statistički značajnu razliku, što naglašava potrebu za daljnjim istraživanjima (16).

Neurološki ishodi nakon KPR-a i dalje ostaju jedno od glavnih područja zabrinutosti u vezi s primjenom adrenalina. Istraživanja na životinjskim modelima, poput studije Deakina i suradnika, pokazala su da adrenalin može pogoršati mikrocirkulaciju i cerebralnu oksigenaciju tijekom KPR, što može negativno utjecati na neurološke ishode (22). Slični rezultati objavljeni su i od strane Hawkesa, koji je ukazao na povećan rizik od ozbiljnog neurološkog oštećenja kod preživjelih bolesnika koji su primili adrenalin, s gotovo dvostruko većim učestalosšću u usporedbi s kontrolnom skupinom (23). Ovi nalazi slažu se s rezultatima PARAMEDIC-2 studije, u kojoj je kod bolesnika koji su primili adrenalin zabilježena gotovo dvostruko veća učestalost teškog neurološkog oštećenja (19).

Doze adrenalina

Devedesetih godina prošlog stoljeća provedene su studije o tome je li učinkovitija standardna od visoke doze adrenalina koje su donijele oprečne rezultate. Usporedbom doze od 0,02 mg/kg adrenalina s dozom od 0,2 mg/kg, nije pronađena statistički značajna razlika u postizanju ROSC-a, preživljavanju do prijema u bolnicu ili otpustu kao niti u neurološkom ishodu (24). Istovjetne rezultate pokazala je usporedba doza od 7 mg i 1 mg adrenalina u studiji koju su proveli Stiell i sur., čak i kada se uzima u obzir izvanbolnički srčani zastoj u odnosu na bolnički srčani zastoj (25). Studija Dumasa i sur. ukazala je kako uz povećanje doze adrenalina postoji postupno smanjenje vjerojatnosti preživljavanja s dobrim neurološkim ishodom (26). Gueugniauda i sur. ustanovili su statistički značajnu razliku u ROSC-u i preživljavanju do prijema u bolnicu između bolesnika koji su primili do 15 doza od 5 mg adrenalina u usporedbi sa standardnom dozom od 1 mg, ali bez statistički značajne razlike u preživljavanju do otpusta ili neurološkom ishodu (27). Slično tome, doza od 15 mg adrenalina u usporedbi sa standardnom dozom također je pokazala poboljšanje učestalosti postizanja ROSC-a, ali ne i preživljavanja do otpusta iz bolnice niti neurološkog ishoda (28). Iako početne ili eskalirajuće visoke doze epinefrina ponekad poboljšavaju ROSC i rano preživljavanje, osam randomiziranih kliničkih studija i više od 9.000 bolesnika sa srčanim zastojem nije rezultiralo poboljšanjem preživljavanja do otpusta iz bolnice ili neurološkog ishoda. Retrospektivne studije sugeriraju da visoke kumulativne doze adrenalina mogu biti povezane s lošijim hemodinamskim i neurološkim ishodima, ali to nije dokaz uzročne povezanosti (29).

Unatoč povećanju učestalosti povratka spontane cirkulacije, primjena adrenalina tijekom KPR-a ne dovodi do značajnog poboljšanja dugoročnog preživljavanja niti neuroloških ishoda, a rizik od ozbiljnog neurološkog oštećenja može biti veći kod preživjelih bolesnika.

Meta-analiza šest randomiziranih kontroliranih studija koja uspoređuju standardnu dozu adrenalina (1 mg) s višom dozom adrenalina (> 1 mg) zaključila je kako standardna doza adrenalina ima nižu stopu ROSC-a i preživljavanja do prijema u bolnicu. Međutim, nije bilo razlike u preživljenju do otpusta iz bolnice ili neurološki povoljnog ishoda (30). Iako adrenalin može povećati ROSC, postoje ograničeni dokazi da ponavljane doze adrenalina poboljšavaju ukupno preživljenje, a sve je više dokaza o neurološki nepovoljnom ishodu kod preživjelih. U studiji provedenoj tijekom jednogodišnjeg razdoblja kod 3151 bolesnika koji su primili jednu ili više doza adrenalina (bolus od 1 mg) tijekom izvanbolničkog srčanog zastoja, praćeni su ishodi preživljavanja do otpusta iz bolnice i godinu dana nakon otpusta. Ponovljene doze adrenalina bile su povezane sa smanjenim izgledima za preživljavanje do otpusta iz bolnice i godinu dana nakon otpusta. Niti jedan bolesnik nije preživio nakon što je primio više od deset doza adrenalina (31). Retrospektivna kohortna studija Boivina i sur. ukazuje na smanjenje povoljnih neuroloških ishoda s povećanjem broja doza adrenalina. Sedam ili više doza gotovo uvijek je bilo neučinkovito, sugerirajući potrebu za opreznom procjenom koristi nastavka KPR-a (32). Iako su neke studije pokazale kako veći broj doza adrenalina dovode do lošijih ishoda KPR-a, točna doza adrenalina iznad koje ne bi bilo daljnje koristi nije jasna.

Nekoliko nedavnih istraživanja ispitivalo je učinak kumulativnih doza adrenalina tijekom izvantjelesne kardiopulmonalne reanimacije. Garcia i suradnici izvijestili su kako su bolesnici sa srčanim zastojem koji su primili nisku dozu (manje od 3 mg adrenalina) imali povoljnije neurološke ishode u usporedbi s onima koji su primili visoku dozu (više od 3 mg) (33). Lamhaut i sur. pokazali su kako su bolesnici koji su primili manje od 5 mg adrenalina tijekom ECPR-a imali značajno bolje stope preživljavanja (34). Ovi rezultati otvaraju prostor za istraživanje optimizacije doziranja adrenalina tijekom KPR.

Razvidno je kako dostupni podaci više ne podržavaju neupitnu upotrebu standardnih doza kod svih uzroka srčanog zastoja. Korištenje adrenalina treba se temeljiti na dokazima, uz ravnotežu između učinkovitosti i nuspojava. Potrebna su prospektivna randomizirana klinička istraživanja kako bi se istražile potencijalne terapijske alternative adrenalinu i uvele u kliničku praksu, te evaluirale modifikacije doziranja i vremena primjene s ciljem određivanja racionalne upotrebe adrenalina (35).

Vremenski okviri primjene adrenalina

Vrijeme primjene adrenalina ključno je za povećanje šanse za ROSC, poboljšanje preživljavanja i postizanje povoljnog neurološkog ishoda.

Studije koje su pokušale odrediti optimalno vrijeme primjene adrenalina dale su različite rezultate. Dvije studije analizirale su podatke o vremenu primjene adrenalina u bolesnika s izvanbolničkim srčanim zastojem. Rezultati su pokazali kako ranija primjena adrenalina, osobito unutar prvih 10–20 minuta, povećava vjerojatnost ROSC-a i smanjuje neurološko oštećenje (36,37). Nadalje, Hayakawa i sur. zaključili su kako svaka minuta ranije primjene adrenalina povećava šansu povoljnog neurološkog ishoda za 1,1 puta (38). Retrospektivna analiza provedena u 570 bolnica u Americi, ispitivala je ishode ovisno o vremenu primjene prve doze adrenalina kod bolesnika sa srčanim zastojem u izvanbolničkim uvjetima i početnim ritmom električne aktivnosti bez pulsa ili asistolije. Autori su ukazali na prednosti primjene adrenalina unutar 1-3 minute što je povezano s boljim ROSC-om i neurološkim ishodom kod bolesnika s asistolijom ili električnom aktivnosti bez pulsa (39). Druga slična analiza ustanovila je kako je primjena adrenalina unutar 10 minuta od dolaska hitne medicinske službe bolesniku s izvanbolničkim srčanim zastojem i ritmovima koji se ne defibriliraju povezana s najvišom učestalošću preživljavanja, dok je svaka dodatna minuta kašnjenja u primjeni smanjivala izglede za preživljavanje do otpusta iz bolnice za 4 % (40). Multicentrična opservacijska studija provedena u Japanu utvrdila je slične rezultate kod bolesnika s ventrikulskom fibrilacijom, pri čemu je preživljavanje s očuvanim neurološkim funkcijama bila značajno veća ako je adrenalin primijenjen unutar 10 minuta nakon srčanog zastoja u usporedbi s njegovim izostankom. Autori zaključuju kako učinkovitost adrenalina nakon izvanbolničkog srčanog zastoja ovisi o vremenu primjene te, ako se primjenjuje u ranoj fazi, poboljšavaju se neurološki ishodi kod bolesnika s ventrikulskom fibrilacijom. Nije bilo statistički značajne razlike u preživljavanju ako je primjena adrenalina uslijedila 10 minuta nakon nastanka srčanog zastoja (41). Retrospektivna studija Sigala i sur. imala je za cilj istražiti povezanost vremena primjene i doze adrenalina s ROSC-om i neurološkom funkcijom nakon KPR-a. Analizirani su slučajevi srčanog zastoja u izvanbolničkom uvjetima koji su trajali duže od 10 minuta sa srčanim ritmovima koji se defibriliraju. Rezultati ukazuju kako rana primjena adrenalina povećava učestalost preživljavanja do otpusta iz bolnice, ali ne jamči povoljan neurološki ishod. Također, niža ukupna doza adrenalina prije postizanja ROSC-a povezana je s boljim neurološkim ishodima (42). Novije kohortne studije s podudarnim rezultatima također su pokazale veću učestalost preživljavanja u bolesnika koji su rano primili adrenalin, neovisno radi li se o srčanim ritmovima koji se defibriliraju ili onima koji se ne defibriliraju (43,44). Nasuprot tome, u retrospektivnoj opservacijskoj studiji provedenoj u Michiganu, nije zabilježeno poboljšanje preživljavanja do otpusta iz bolnice (45). Sekundarna analiza PARAMEDIC-2 studije ustanovila je kako vrijeme primjene adrenalina nema značajan učinak na preživljavanje ili neurološke ishode (19,46).

Studija Grunaua i sur. koja se usmjerila na intervale doziranja adrenalina tijekom neprekinutih kompresija prsnog koša zabilježila je kako kraći intervali (manje od svakih 3 minute) poboljšavaju preživljavanje i neurološke ishode nakon izvanbolničkog srčanog zastoja, u usporedbi s intervalima od 3-4, 4-5 i više od 5 minuta (47). Međutim, analize rezultata dvije retrospektivne opservacijske studije bolničkog srčanog zastoja kod odraslih drugačiju su dinamike jer je češće doziranje adrenalina, uključujući trenutne smjernice (svakih 3-5 minuta), dovelo do lošijih ishoda kod kako kod srčanih ritmova koji se defibriliraju, tako i kod srčanih ritmova koji se defibriliraju (48,49). Opservacijska studija iz 2016. godine usmjerila se na bolesnike u bolničkim uvjetima s perzistentnim srčanim ritmom koji se defibrilira i analizirala je interval primjene adrenalina u odnosu na defibrilaciju. Autori su zaključili kako je primjena adrenalina unutar dvije minute nakon prve defibrilacije povezana sa smanjenim izgledima za ROSC, smanjenim izgledima za preživljavanje do otpusta iz bolnice kao i dugoročno preživljavanjem uz dobre neurološke ishode (6). Ovi rezultati ističu potrebu za boljim razumijevanjem interakcije između defibrilacije i primjene adrenalina. Nasuprot tome, Kawakami i sur. su, u nedavnom istraživanju o povezanosti intervala defibrilacije i primjene adrenalina te kratkoročnih ishoda u bolesnika s izvanbolničkim srčanim zastojem, izvjestili o prednosti ranije primjene adrenalina čak i u bolesnika s ritmovima koji se defibriliraju. Duži intervali između defibrilacije i

primjene adrenalina (više od dvije minute) bili su povezani s lošijim ishodima, uključujući stope ROSC-a, 30-dnevno preživljavanje i neurološke ishode (50).

Sveukupno, rana primjena adrenalina, kraći intervali između doza, te defibrilacija prije primjene adrenalina mogu poboljšati preživljavanje, ali to možda neće rezultirati značajno povoljnim neurološkim ishodima.

Rana primjena adrenalina i kraći intervali između doza mogu poboljšati preživljavanje, no često ne dovode do značajnih poboljšanja u neurološkim ishodima.

Zaključak

Adrenalin je dugi niz godina bio ključni lijek u naprednim postupcima održavanja života, jer povećava šanse za povratak spontane cirkulacije i preživljavanje do prijema u bolnicu i otpusta. Međutim, učinci adrenalina na dugoročno preživljavanje i neurološke ishode i dalje su predmet rasprava. Istraživanja ukazuju da adrenalin može povećati rizik od ozbiljnih neuroloških oštećenja zbog negativnog utjecaja na mikrocirkulaciju i oksigenaciju mozga. Zbog toga se opravdanost njegove primjene tijekom kardiopulmonalne reanimacije sve više dovodi u pitanje, a njegova korisnost i učinkovitost ponovno se procjenjuju. Unatoč brojnim istraživanjima koja su pokušala odgovoriti na ova pitanja, rezultati su i dalje različiti. Mnoge studije provedene su na životinjskim modelima, čiji rezultati nisu uvijek primjenjivi na ljude zbog razlika u strukturi i funkciji.

Prema Međunarodnom konsenzusu o znanosti KPR-a i hitne kardiovaskularne skrbi, postoje značajne praznine u dostupnim podacima o primjeni adrenalina u KPR-u. Iako su provedene velike randomizirane kontrolirane studije, još uvijek postoji nesigurnost u vezi s njegovim utjecajem na neurološke ishode, bilo povoljne ili nepovoljne. Nisu postojale studije koje bi se bavile pitanjem optimalne doze adrenalina za različite bolesnike, optimalnog vremena primjene u odnosu na defibrilaciju, optimalnih intervala doziranja, niti evaluacije primjene adrenalina kod bolničkog srčanog zastoja. Zbog tih nedostataka, trenutni dokazi nisu dovoljno jaki da potvrde ili isključe učinkovitost adrenalina, zbog čega se on i dalje preporučuje u smjernicama Europskog vijeća za reanimatologiju u standardnoj dozi od 1 mg iv./io. svakih 3 do 5 minuta tijekom KPR.

Kako bi se razjasnila učinkovitost adrenalina i odgovorilo na postojeće prijepore, nužno je provesti multicentrične randomizirane kontrolirane studije. Osim toga, buduća istraživanja trebala bi se usmjeriti na dugoročne ishode koji nadmašuju samo povratak spontane cirkulacije, te na razvoj individualiziranog pristupa koji uzima u obzir specifične kliničke okolnosti kako bi se poboljšali funkcionalni ishodi za bolesnike sa srčanim zastojem.

S velikim nestrpljenjem ove godine očekujemo nove smjernice ERC-a u nadi kako će možda dati bar neke odgovore na kontroverze u svezi primjene adrenalina tijekom KPR.

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REVIEW ARTICLE / PREGLEDNI ČLANAK

THE ROLE OF FAITH IN SUPPORTING TERMINALLY ILL PATIENTS IN EMERGENCY DEPARTMENT

ULOGA VJERE U PODRŠCI TERMINALNIM BOLESNICIMA U HITNOM BOLNIČKOM PRIJEMU

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Abstract

This article explores the role of faith in supporting terminally ill patients and emergency department (ED) staff, emphasizing the benefits of spiritual care in enhancing patient well-being and staff resilience. Practical recommendations are outlined.

Key words: faith; terminally ill; emergency department

Sažetak

Ovaj članak istražuje ulogu vjere u podršci terminalno bolesnim pacijentima i osoblju u hitnom bolničkomk prijemu, naglašavajući prednosti duhovne skrbi u poboljšanju dobrobiti pacijenata i otpornosti osoblja. Navedene su praktične preporuke.

Ključne riječi: vjera; terminalni bolesnik; odjel hitne medicine

Introduction

The role of faith in supporting terminally ill patients and healthcare staff in emergency departments (EDs), as well as in palliative and hospice care settings, is increasingly recognized as essential to comprehensive, compassionate healthcare. EDs, often the front lines for those in their final stages of life, present unique challenges and opportunities to incorporate spiritual care, an aspect that has long been under-emphasized in modern emergency medicine. In this short article, we discuss the multifaceted ways faith can serve as a critical component for patients' and staff's resilience and well-being, while advocating for structural changes in ED settings to facilitate a more holistic approach to patient care.

Faith as a Source of Comfort and Meaning for Terminally Ill Patients

For terminally ill patients, spirituality and faith often serve as vital sources of strength, comfort, and existential meaning, particularly in high-stress environments like the ED. Studies such as Puchalski (1) suggest that spiritual beliefs can profoundly impact how patients cope with their illness, perceive their suffering, and face their mortality. In the clinical setting, acknowledgment of a patient's spiritual beliefs can contribute to preserving their dignity and enhancing their sense of personhood amidst the intense clinical interventions often seen in the ED.

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The Importance of Spiritual Care in Improving Quality of Life and Car

Research underscores the positive association between spiritual care and quality of life for terminally ill patients. In a study by Balboni et al. (2), spiritual care was linked to improved quality of life near death, illustrating that patients who receive spiritual support often experience greater peace, acceptance, and readiness. However, the study also identified a concerning gap: spiritual care remains inconsistently provided in many medical settings, including EDs, where the focus is traditionally on acute and immediate medical interventions rather than on holistic patient needs.

> Faith and spirituality provide comfort and meaning for terminally ill patients in emergency departments, helping them preserve dignity and accept their mortality.

Faith as a Support Mechanism for ED Staff

The demanding environment of emergency medicine exposes healthcare providers to high levels of stress, frequent encounters with trauma, and complex emotional challenges (3). Faith can play a critical role in enhancing resilience among ED staff, providing them with a buffer against burnout and compassion fatigue (4) For instance, Rushton et al. (5) found a strong correlation between spiritual well-being and resilience in high-intensity healthcare settings, suggesting that personal faith or spirituality could be a key resource for staff coping mechanisms.

Barriers to Integrating Spiritual Support in EDs

Despite its benefits, several systemic and practical barriers hinder the integration of faith-based support in EDs:

1. Time Constraints: The fast-paced, urgent nature of emergency care often limits time available for addressing patients' spiritual needs.
2. Lack of Training: Many healthcare providers feel inadequately prepared to engage in spiritual conversations with patients.
3. Concerns About Professional Boundaries: Healthcare professionals may worry about overstepping boundaries.
4. Limited Resources: EDs frequently lack access to chaplains or spiritual care providers.

Expanding the Role of Faith-Based Interventions in Diverse ED Settings

Given the diversity of patients who frequent EDs, understanding the varied roles that faith and spirituality play across different cultural and religious backgrounds is essential. This diversity adds a layer of complexity to spiritual care, as each patient's experience of faith can significantly differ. For example, studies show that patients from religious minority groups may rely more heavily on their faith when confronted with serious illnesses, partly due to a lack of representation in healthcare or limited access to culturally aligned resources. Consequently, EDs that actively incorporate a broader cultural and spiritual sensitivity in their approach are likely to enhance trust, patient satisfaction, and the perceived quality of care (6).

Moreover, in some cases, spiritual beliefs may influence patients' decisions about medical treatments, including end-of-life care preferences (12). Healthcare providers who understand and respect these beliefs, even when they differ from conventional medical perspectives, may find it easier to establish rapport and deliver care aligned with patients' values. A study by Curlin et al. (7) illustrated that clinicians who identify as spiritual themselves were more willing to engage in these sensitive discussions, suggesting that shared values or respect for spirituality can play a positive role in clinician-patient relationships (8,9).

> Integrating spiritual care in EDs improves the quality of life for terminally ill patients, yet remains underutilized, highlighting a need for structural changes to prioritize holistic care.

Innovative Approaches: Integrating Technology in Spiritual Care

Technology offers new avenues for enhancing spiritual care in EDs, particularly through virtual support. For instance, some hospitals have experimented with "telechaplaincy," where spiritual care providers or chaplains provide virtual support via video calls, reducing the physical presence needed and enabling remote support in time-sensitive scenarios. Telechaplaincy services can be especially valuable in rural or understaffed EDs, where chaplain access is limited. Furthermore, digital platforms can facilitate the use of audio meditations or prayer sessions for patients who find comfort in such practices, thus broadening accessibility for patients of various faiths.

Future research might explore the role of artificial intelligance (AI) in spiritual care, particularly how machine learning algorithms could be used to provide real-time spiritual assessments or even suggest spiritual resources tailored to individual patient profiles. These technological advances could offer valuable adjuncts to in-person spiritual care, though ethical considerations must be addressed to ensure respect for privacy and cultural sensitivity.

Integrating faith-based support in emergency departments enhances holistic patient care and staff resilience, addressing critical emotional and spiritual needs during high-intensity situations.

The Psychological Benefits of Faith-Based Interventions on Patient Outcomes

Faith-based interventions can also positively affect psychological outcomes in patients facing terminal diagnoses. For example, when patients engage in guided spiritual practices such as prayer, meditation, or conversation with chaplains, studies show reductions in anxiety and improved emotional resilience. Puchalski (1) notes that spiritual practices may help patients confront existential fears about death, facilitating a sense of peace and purpose even during intense medical treatments. For ED staff, understanding these benefits provides an additional layer of motivation to respect and promote spiritual care.

Expanding Staff Training on Spiritual and Cultural Competence

While spiritual care has its complexities, there are practical steps for enhancing staff training in EDs to address this need. Integrating regular workshops on cultural competence, spiritual sensitivity, and communication strategies allows staff to gain confidence in navigating conversations about faith with patients. Furthermore, including spiritual care training in medical and nursing curriculums can help future healthcare providers develop a more nuanced approach to holistic care early in their careers. By normalizing these conversations, healthcare providers may also find themselves better equipped to handle emotionally intense situations, thereby reducing personal burnout. (10)

Institutional Policy and Structural Support for Faith-Based Care

Effective implementation of spiritual support requires institutional buy-in. This may involve revising hospital policies to accommodate spiritual care within emergency protocols, establishing partnerships with community faith organizations, or even appointing spiritual care coordinators within EDs. Some EDs may benefit from policy adjustments that allow for flexible practices, such as permitting family members or spiritual advisors to remain with patients during critical moments, where feasible, or allowing brief moments of prayer as part of end-of-life protocols (11).

Moving Towards Holistic and Inclusive Healthcare

Faith and spirituality remain deeply personal yet universally impactful aspects of human life. Integrating these aspects into emergency care signals a shift towards a more inclusive healthcare model, one that respects the full scope of patient needs. As medicine continues to advance technologically and ethically, acknowledging the role of faith can bridge gaps in care, fostering an environment of empathy, understanding, and mutual respect. Such a model not only serves terminally ill patients but strengthens the fabric of emergency care, promoting resilience among healthcare staff and contributing to a compassionate, person-centered approach (12).

Practical Recommendations to Enhance Spiritual Care in EDs

To address these challenges, several strategies can be implemented to improve the integration of faith-based support in EDs:

1. Implement Brief Spiritual Assessments
2. Increase Staff Training
3. Collaborate with Chaplains
4. Create Sacred Spaces
5. Develop Evidence-Based Protocols
6. Support Staff Spirituality

Future Research Directions

Further research is essential to develop and validate best practices for integrating spiritual care into emergency medicine.

Future studies could explore:

1. The impact of spiritual care on patient outcomes in emergency settings
2. Effective methods for rapid spiritual assessment in time-sensitive situations
3. The role of technology in providing spiritual support, including telechaplaincy in EDs
4. Long-term effects of spiritual care interventions on staff resilience and job satisfaction

Conclusion

Faith serves as a vital resource for both patients and healthcare providers in EDs, offering a source of comfort, meaning, and resilience during some of life's most challenging moments. Acknowledging and integrating spirituality within emergency medicine not only improves the quality of end-of-life experiences but also supports the well-being of ED staff.

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