Heydeov sindrom – nerijetko zapostavljeni patofiziološki slijed zbivanja u svakodnevnoj kliničkoj praksi

Heyde Syndrome – An Often-Neglected Pathophysiological Course in Daily Clinical Practice

Daren Lučinger[1]*, Nenad Lakušić[1,2,3], Duško Cerovec[1,2,3], Krunoslav Fučkar[1,3], Ljubica Vincelj Šalković[1]

[1]Specijalna bolnica za medicinsku rehabilitaciju Krapinske Toplice, Krapinske Toplice, Hrvatska

[2]Fakultet za dentalnu medicinu i zdravstvo Osijek, Sveučilište J. J. Strossmayer Osijek, Osijek, Hrvatska

[3]Medicinski fakultet Osijek, Sveučilište J. J. Strossmayer Osijek, Osijek, Hrvatska

[1]Special Hospital for Medical Rehabilitation Krapinske Toplice, Krapinske Toplice, Croatia

[2]Faculty of Dental Medicine and Health Osijek, J. J. Strossmayer University of Osijek, Osijek, Croatia

[3]Faculty of Medicine Osijek, J. J. Strossmayer University of Osijek, Osijek, Croatia

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SAŽETAK: Klasični trijas simptoma aortalne stenoze – angina pektoris, zatajivanje srca te sinkopa, kliničarima je dobro poznat, no manifestacije aortalne stenoze na druge organske sustave često ostaju neprepoznate. Angiodisplazije probavnog trakta, kao i aortalna stenoza, degenerativna su bolest, a samim time češće u starijoj populaciji. Heydeov sindrom obuhvaća trijadu aortalne stenoze, stečene koagulopatije (von Willebrandov sindrom tipa 2A) i sideropenične anemije koja nastaje kao posljedica krvarenja iz gastrointestinalnih (GI) angiodisplazija ili iz nepoznatog sijela. Stečena koagulopatija nastaje zbog degradacije multimera von Willebrandova faktora (vWf) i uzrokovana je stresom smicanja na stenotičnoj aortalnoj valvuli. Zamjena aortalne valvule dovodi do oporavka koncentracije multimera vW faktora i posljedične rezolucije gastrointestinalnoga krvarenja i sideropenične anemije. U populaciji bolesnika s aortalnom stenozom razvoj sideropenične anemije treba pobuditi sumnju na Heydeov sindrom, ali i kod bolesnika s dokazanim krvarenjem iz angiodisplazija GI trakta ili nerazjašnjenim GI krvarenjem nakon endoskopske obrade potrebno je obaviti ehokardiogram s obzirom na mogućnost postojanja aortalne stenoze.

SUMMARY: The classic triad of aortic stenosis symptoms – angina pectoris, heart failure, and syncope - is well-known among clinicians, but manifestations of aortic stenosis on other systems often remain unrecognized. Gastrointestinal (GI) angiodysplasia, like aortic stenosis, is degenerative disease and both entities are more common in older patients. Heyde syndrome refers to a triad of aortic stenosis, acquired coagulopathy (von Willebrand syndrome type 2A), and sideropenic anemia due to bleeding from gastrointestinal angiodysplasia or from an idiopathic site. Acquired coagulopathy arises from degradation of vWF multimers by the shear stress across the stenotic aortic valve. Aortic valve replacement leads to rise in vW factor multimers and ultimate resolution of gastrointestinal bleeding and sideropenic anemia. In patients with established aortic stenosis, development of iron deficiency anemia should raise the possibility of Heyde syndrome, but patients with GI bleeding with presence of angiodysplasia or failure of endoscopy to find the site of GI bleeding should also be evaluated for aortic stenosis.

KLJUČNE RIJEČI: Heydeov sindrom, aortalna stenoza, anemija, krvarenje, von Willebrandov faktor.

KEYWORDS: Heyde syndrome, aortic stenosis, anemia, bleeding, von Willebrand factor.

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***ADDRESS FOR CORRESPONDENCE**: Daren Lučinger, Specijalna bolnica za medicinsku rehabilitaciju Krapinske Toplice, Gajeva 2, HR-49217 Krapinske Toplice, Croatia. / Phone: + 385-49-383-100 / E-mail: darenlucinger@gmail.com

ORCID: Daren Lučinger, https://orcid.org/0000-0001-8848-0472 • Nenad Lakušić, https://orcid.org/0000-0002-2329-2582 Duško Cerovec, https://orcid.org/0000-0002-5675-4202 • Krunoslav Fučkar, https://orcid.org/0000-0002-2723-8356 Ljubica Vincelj Šalković, https://orcid.org/0000-0003-2432-802X

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Degenerativna aortalna stenoza najčešća je valvularna bolest u starijih ljudi i jedan od vodećih uzroka morbiditeta i mortaliteta u toj populaciji. Prevalencija raste s godinama, a dostiže 2 – 7 % u ljudi u dobi nakon 65. godine[1]. Klasični trijas simptoma aortalne stenoze – angina pektoris, zatajivanje srca te sinkopa[2], kliničarima je dobro poznat, no manifestacije aortalne stenoze na druge organske sustave (npr. gastroenterološke ili hematološke) često ostaju neprepoznate. Angiodisplazija je najčešći vaskularni poremećaj gastrointestinalnoga trakta[2].

Degenerative aortic stenosis is the most common valvular disease in the elderly and one of the leading causes of morbidity and mortality in that population. The prevalence increases with age and reaches 2-7% in those above 65 years of age[1]. The classic triad of aortic stenosis symptoms – angina pectoris, heart failure, and syncope[2], is well-known to clinicians, but manifestations of aortic stenosis on other systems (e.g. gastroenterological or hematological) often remain unrecognized. Angiodysplasia is the most common vascular disorder of

Riječ je o degenerativnoj bolesti krvnih žila, a 70 % angiodisplazija lokalizirano je u području cekuma i uzlaznog kolona. Nakon divertikuloze, drugi je najčešći uzrok krvarenja iz donjeg dijela probavnoga trakta u osoba starijih od 60 godina[3].

Poveznicu između aortalne stenoze i angiodisplazije kolona, s obzirom na to da su obje degenerativne bolesti, a samim time češće u starijoj populaciji, teško je objasniti. Prvi ju je 1958. godine zamijetio i opisao Edward Heyde, objavivši 10 slučajeva kalcificirane aortalne stenoze i teškoga gastrointestinalnog krvarenja. Heydeov sindrom danas podrazumijeva trijadu aortalne stenoze, stečene koagulopatije (von Willebrandov sindrom tipa 2A) i sideropenične anemije kao posljedice krvarenja iz gastrointestinalnih angiodisplazija ili nepoznatog sijela[4].

Pate *i sur.* u retrospektivnom su istraživanju utvrdili statistički značajnu poveznicu između aortalne stenoze i gastrointestinalnoga krvarenja za koje se pretpostavilo da je posljedica angiodisplazija[5]. Još jedna retrospektivna studija Greensteina *i sur.*, koja je uključila 3623 bolesnika s aortalnom ili mitralnom stenozom, pokazala je da je kvarenje iz gastrointestinalnoga trakta mnogo češće udruženo s aortalnom stenozom[6]. Aortalna stenoza ima dugo asimptomatsko razdoblje, a intestinalna angiodisplazija ne rezultira uvijek značajnom anemijom, pa stoga točna prevalencija Heydeova sindroma nije poznata[4]. Postoji više patofizioloških mehanizama kojima se može objasniti kako aortalna stenoza uzrokuje ili pospješuje krvarenje iz angiodisplazija. Neki su od njih: simpatetička vazodilatacija intestinalnih krvnih žila kao odgovor na kroničnu hipoksiju ili kolesterolske emboluse s degenerativne aortalne valvule te deficijencija multimera von Willebrandova faktora visoke molekularne težine koja je ujedno i najuvjerljivija[7]. Stečeni von Willebrandov sindrom-2A (vWS-2A) nastaje degradacijom multimera von Willebrandova faktora (vWF) zbog stresa smicanja duž stenotične aortalne valvule. Nefiziološka degradacija velikih multimera vWF-a koji su inače najaktivniji u vrijeme stvaranja trombocitnog ugruška odgovorna je za koagulopatiju kod Heydeova sindroma[8], što sve pospješuje i česta konkomitantna antitrombocitna ili antikoagulantna terapija u te skupine bolesnika. Vjerojatno je potreban gradijent tlaka od najmanje 50 mmHg nad aortalnom valvulom kako bi nastala navedena koagulopatija[9]. Aortalna stenoza nije jedini „kardiogeni" uzrok deficita vWF-a, a ostali kardiovaskularni uzroci stečenoga von Willebrandova sindroma jesu: hipertrofična kardiomiopatija (s opstrukcijom izgonskoga trakta lijeve klijetke), disfunkcionalni protetički zalistci, ventrikularni septalni defekt, perzistentni ductus arteriosus i sustav potpore lijevom ventrikulu[10].

Zlatni standard za dijagnozu vWS-2A jest gel elektroforeza vWF[5]. Patognomoničan je nedostatak velikih vWF multimera na SD-agaroza elektroforezi[11].

Liječenje Heydeova sindroma zahtijeva multidisciplinarni pristup, a podrazumijeva sljedeće modalitete: medikamentnu terapiju, endoskopsko i kirurško liječenje promjena unutar gastrointestinalnoga trakta te zamjenu aortalne valvule protetičkom[7]. Klasična terapija von Willebrandove bolesti dezmopresinom, oktreotidom ili supstitucijom vWF-a i faktora VIII obično je neučinkovita u liječenju vWF sindroma tipa 2A, iako se supstitucija prije navedenih koagulacijskih faktora neposredno prije operativnog liječenja može razmotriti u bolesnika koji imaju prolazni oporavak u aktivnosti vW faktora na testnu dozu[5].

the gastrointestinal tract[2]. It is a degenerative disease of the blood vessels, and 70% of angiodysplasias are localized in the cecum and ascending colon. After diverticulosis, it is the second most common cause of bleeding from the lower digestive tract in persons older than 60[3].

The link between aortic stenosis and angiodysplasia of the colon is difficult to explain, given that they are both degenerative diseases and thus more common in the older population. It was first noticed and described in 1958 by Edward Heyde, who published 10 cases of calcified aortic stenosis and severe gastrointestinal bleeding. Today, Heyde syndrome refers to the triad of aortic stenosis, acquired coagulopathy (von Willebrand syndrome type 2A), and sideropenic anemia due to bleeding from gastrointestinal angiodysplasia or from an idiopathic site[4].

Pate et al. conducted a retrospective study that found a statistically significant association between aortic stenosis and gastrointestinal bleeding which was assumed to be the result of angiodysplasia[5]. Another retrospective study by Greenstein et al. that included 3623 patients with aortic or mitral stenosis showed that bleeding from the gastrointestinal tract was statistically significantly more likely to be associated with aortic stenosis[6]. Aortic stenosis has a long asymptomatic period, and intestinal angiodysplasia does not always result in significant anemia, so the exact prevalence of Heyde syndrome remains unknown[4]. There are multiple pathophysiological mechanisms that could explain how aortic stenosis causes or exacerbates bleeding from angiodysplasia. Some of these include: sympathetic vasodilatation of intestinal blood vessels as a response to chronic hypoxia or cholesterol emboli sms from a degenerative aortic valve and degradation of von Willebrand factor (vWF) high molecular weight multimers, the latter being the most convincing explanation[7]. Acquired von Willebrand syndrome type 2A (vWS-2A) is caused by vWF multimer degradation due to shear stress across the stenotic aortic valve. Non-physiological degradation of large vWF multimers that are normally most active during thrombus formation is responsible for coagulopathy in Heyde syndrome[8], all of which is also exacerbated by the common concomitant antithrombotic or anticoagulation therapy in this patient group. It is likely that a pressure gradient of at least 50 mmHg over the aortic valve is necessary to develop this coagulopathy[9]. Aortic stenosis is not the only "cardiogenic" cause of vWF deficiency, and other cardiovascular causes of acquired von Willebrand syndrome are: hypertrophic cardiomyopathy (with left ventricular outflow tract obstruction), dysfunctional prosthetic valves, ventricular septal defect, persistent ductus arteriosus, and left ventricular support systems[10].

The gold standard for vWS-2A diagnosis is vWF gel electrophoresis[5]. The absence of large vWF multimers in SDS-agarose gel electrophoresis is pathognomonic[11].

Treatment of Heyde syndrome requires a multidisciplinary approach and includes the following treatment modalities: medication therapy, endoscopic and surgical treatment for changes within the gastrointestinal tract, and prosthetic replacement of the aortic valve[7]. The classic treatment of von Willebrand disease with desmopressin, octreotide, or substitution of vWF and factor VIII is usually ineffective in treatment of vWF syndrome type 2A, although substitution of these coagulation factors immediately prior to surgical treatment can be considered in patients with transitory recovery in vW factor activity after a test dose[5].

U bolesnika koji su liječeni resekcijom angiodisplastično promijenjenoga crijeva obično je došlo do rekurencije krvarenja iz drugih dijelova crijeva ili na drugim sluznicama, dok zamjena aortalne valvule protetičkom rješava poremećaj na razini koagulacijske kaskade i dovodi do rezolucije anemije[4]. Yoshida *i sur.* upozorili su na elektroforezom dokazan deficit velikih multimera vW faktora u bolesnika s aortalnom stenozom te postoperativni oporavak koncentracije navedenih multimera. Dakle, zamjena aortne valvule dovodi do oporavka koncentracije multimera vW faktora i posljedične rezolucije gastrointestinalnog krvarenja[12]. Retrospektivna studija koje je uključila 91 bolesnika s aortalnom stenozom i nerazjašnjenim gastrointestinalnim krvarenjem pokazala je da je krvarenje prestalo u čak 93 % bolesnika nakon kirurške ugradnje aortalnoga umjetnog zalistka, za razliku od samo 5 % bolesnika koji su liječeni drugim metodama (s resekcijom crijeva ili bez nje)[5,13]. Pojedini autori čak predlažu da se u bolesnika s aortalnom stenozom krvarenje iz gastrointestinalnih angiodisplazija te dokazani stečeni vWS postave kao jedna od indikacija za kardiokirurško liječenje, a procjena težine vWS – 2A kao jedan od čimbenika koji određuju pravo vrijeme za zahvat[5]. Oralna antikoagulantna terapija nosi rizik od rekurencije krvarenja nakon operativne zamjene stenotične aortalne valvule. Biološki protetički zalistci uglavnom ne zahtijevaju dugoročnu antikoagulantnu terapiju, za razliku od mehaničkih. Načelno, ugradnja bioprotetičkog zalistka na aortalnu poziciju trebala bi biti izbor u bolesnika starijih od 65 godina, ali i u bolesnika u kojih je dugoročna antikoagulantna terapija kontraindicirana zbog visokog rizika od krvarenja (npr. prethodna krvarenja, komorbiditeti...)[1]. Transkateterska implantacija aortalne valvule opcija je u bolesnika s teškom aortalnom stenozom i visokim rizikom od kirurške zamjene zalistka, međutim, preporučena dvojna antiagregacijska terapija 1 – 3 mjeseca nakon zahvata, a pogotovo acetilsalicilatna kiselina povećavaju rizik od gastrointestinalnog krvarenja[10].

Bolesnicima koji odbijaju ili su neprikladni za kirurško ili transkatetersko liječenje stenoze aortnog zalistka preporučuje se suplementacija željeza i transfuzijsko liječenje ovisno o stupnju anemije. Endoskopsko liječenje i oktreotid preporučuju se kod rekurentnih i rezistentnih krvarenja[10].

Neprepoznavanje Heydeova sindroma može dovesti do neželjenoga začaranog kruga. Naime, bolesnici s indikacijom za operativni zahvat na angiodisplastično promijenjenim dijelovima probavnoga trakta (u kojih je endoskopsko liječenje neuspješno i/ili neprikladno) često ne budu podvrgnuti zahvatu zbog aortalne stenoze koja povećava perioperativni mortalitet i morbiditet. S druge strane, bolesnici s indikacijom za zamjenu aortalnog zalistka zbog teške stenoze teže dobivaju odobrenje „heart teama" za operativni zahvat ako je u podlozi nerazjašnjeno ili rekurentno krvarenje iz gastrointestinalnog trakta s posljedičnom anemijom, pogotovo ako je anemija simptomatska i zahtijeva transfuzijsko liječenje.

U populaciji bolesnika s aortalnom stenozom razvoj sideropenične anemije treba pobuditi sumnju na Heydeov sindrom, pogotovo ako se nakon nužne inicijalne endoskopske obrade, osim angiodisplazija, ne nađe jasan uzrok krvarenja iz gastrointerstinalnog trakta te, obrnuto, ako se u bolesnika sa sideropeničnom anemijom, kao posljedicom gastrointestinalnog krvarenja, endoskopskom obradom verificiraju angiodisplazije, nužno je učiniti ehokardiogram kao probir za aortalnu stenozu[4].

Patients treated by resection of the colon with angiodysplastic changes usually had recurring bleeding from other parts of the colon or on other mucosa, whereas prosthetic aortic valve replacement addresses the disorder at the level of the coagulation cascade and leads to resolution of the anemia[4]. Yoshida et al. used electrophoresis to demonstrate a deficit in large vWF multimers in patients with aortic stenosis and the post-surgical recovery in the concertation of these multimers. Therefore, replacement of the aortic valve leads to recovery of vWF factor multimer concentrations and the consequent resolution of gastrointestinal bleeding[12]. A retrospective study that included 91 patients with aortic stenosis and unexplained gastrointestinal bleeding showed that the bleeding stopped in as many as 93% of patients after surgical implantation of an artificial aortic valve, as opposed to only bleeding cessation in only 5% of patients treated with other methods (with or without colon resection)[5,13]. Some authors even recommend that bleeding from gastrointestinal angiodysplasias and established acquired vWS in patients with aortic stenosis should be included as one of the indications for cardiac surgery, while vWS-2A severity assessment should be included as one of the factors determining the right time to perform the procedure[5]. Oral anticoagulant therapy carries the risk of bleeding recurrence after surgical replacement of the stenotic aortic valve. Biological prosthetic valves generally do not require long-term anticoagulation therapy, as opposed to mechanical prostheses. In principle, implantation of a bioprosthetic valve to an aortic location should be the treatment of choice in patients older than 65, but also in patients in whom long-term anticoagulation therapy is contraindicated due to a high risk of bleeding (e.g. previous bleeding, comorbidities, etc.)[1]. Transcatheter aortic valve implantation is an option in patients with severe aortic stenosis and a high risk of surgical valve replacement, however, the recommended dual antiplatelet therapy 1-3 months after the procedure, and aspirin especially, increases the risk of gastrointestinal bleeding[10].

Iron supplements and transfusion treatment are recommended in patients who refuse or are unsuited for surgical or transcatheter treatment of aortic valve stenosis, depending on the level of anemia. Endoscopic treatment and octreotide are recommended in recurrent and resistant bleeding[10].

Failure to recognize Heyde syndrome can lead to an undesirable vicious circle. Patients with indications for a surgical procedure on parts of the digestive tract with angiodysplasia (in which endoscopic treatment is unsuccessful or unsuitable) often do not undergo surgery due to aortic stenosis which increases perioperative mortality and morbidity. On the other hand, patients with indications for aortic valve replacement for severe stenosis have difficulties receiving approval for the surgery from the "heart team" if there is unexplained or recurrent bleeding from the gastrointestinal tract with consequent anemia, especially if the anemia is symptomatic and requires transfusion treatment.

In the population of patients with aortic stenosis, development of sideropenic anemia should raise suspicion of Heyde syndrome, especially if the required endoscopic examination does not reveal a clear cause for gastrointestinal bleeding other than angiodysplasia, or conversely, if endoscopic examination verifies presence of angiodysplasia in patients with sideropenic anemia as a consequence of gastrointestinal bleeding an echocardiogram should be performed to screen for aortic stenosis[4].

Zaključak

Heydeov sindrom često je zapostavljen u svakodnevnoj kliničkoj praksi. Važno je imati na umu i one „atipične" manifestacije čestih bolesti poput aortalne stenoze. Pravodobno prepoznavanje ovog sindroma može dovesti do prekida neželjenoga začaranog kruga i odabira pravilnog modaliteta liječenja, što je u ovom slučaju zamjena aortalne valvule.

Conclusion

Heyde syndrome is often neglected in everyday clinical practice. It is important to keep in mind the "atypical" manifestations of common diseases such as aortic stenosis. Timely recognition of this syndrome can lead to breaking the undesirable vicious circle and choosing the right treatment modality, which is aortic valve replacement.

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