Dijagnostička vrijednost BNP-a kod dijastoličkog zatajivanja srca

Diagnostic value of BNP in diastolic heart failure

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Sažetak

Dijastoličko zatajivanje srca zahvaća otprilike 40-50% bolesnika koji imaju znakove i simptome zatajivanja srca. BNP (engl. *brain natriuretic peptide*, moždani natrijuretski peptid; B-tip natrijuretskog peptida) je srčani neurohormon koji izlučuju mišićne stanice klijetke kao odgovor na povećan tlak ili volumen na kraju dijastole. Sve brojniji dokazi pokazali su da su koncentracije BNP povećane u slučaju zatajivanja srca, te da su te koncentracije osobito važne kod diferencijalne dijagnoze dispneje. Koncentracije BNP su povećane kod dijastoličkog, no obično su niže nego kod sistoličkog zatajivanja srca. Koncentracije BNP su u uzajamnoj vezi sa stupnjem dijastoličke disfunkcije, te su blago povišene među bolesnicima sa simptomima poremećenog opuštanja srčanog mišića, a najviše su među onima s restriktivnim tipom punjenja. Kod asimptomatičnih bolesnika s blagim oblikom dijastoličke disfunkcije, koncentracije BNP mogu biti unutar granica referentnog raspona.

U ovom preglednom članku raspravljamo o dijagnostičkoj vrijednosti BNP u dijagnostici dijastoličkog zatajivanja srca.

Ključne riječi: BNP, dijastoličko zatajivanje srca

Abstract

Diastolic heart failure affects approximately 40%-50% of patients presenting with signs and symptoms of heart failure. Brain natriuretic peptide (BNP) is a cardiac neurohormone secreted from ventricular myocytes in response to increased end-diastolic pressure or volume. Accumulating evidence showed that BNP concentrations are increased in heart failure, and it is especially important in the differential diagnosis of dyspnea. BNP concentrations are increased in diastolic heart failure, but they are typically lower in diastolic than that in systolic heart failure. BNP concentrations are correlated with the stage of diastolic dysfunction, being mild-moderately elevated among patients with evidence of impaired relaxation and highest among those with a restrictive filling pattern. In asymptomatic patients with mild degree of diastolic dysfunction BNP concentrations may be within normal range.

In this review we discuss the diagnostic value of BNP in diastolic heart failure.

Key words: brain natriuretic peptide, diastolic heart failure

Uvod

Zatajivanje srca jedan je od važnih uzroka smrtnosti i pobola u svjetskoj populaciji (1). Može se povezati sa širokim spektrom nepravilnosti u radu lijeve klijetke u raspnu od bolesnika s normalnom veličinom lijeve klijetke i očuvanom istisnom frakcijom (engl. *ejection fraction*), do onih s ozbiljnom dilatacijom i/ili značajno smanjenom sistoličkom funkcijom (2). Otprilike 40-50% bolesnika s dijagnozom zatajivanja srca boluje od dijastoličkog zatajivanja srca s očuvanom sistoličkom funkcijom lijeve klijetke (3). BNP (engl. *brain natriuretic peptide*, moždani natrijuretski peptid; B-tip natrijuretskog peptida) je srčani neurohormon koji izlučuju mišićne stanice klijetke kao odgovor na

Introduction

Heart failure (HF) is an important cause of mortality and morbidity in the population worldwide (1). It may be associated with a wide spectrum of left ventricular (LV) functional abnormalities, which may range from patients with normal LV size and preserved ejection fraction (EF) to those with severe dilatation and/or markedly reduced systolic function (2). Approximately 40%-50% of HF patients have diastolic HF with preserved left ventricular systolic function (3). Brain natriuretic peptide (BNP) is a cardiac neurohormone, secreted from ventricular myocytes in response to increased end-diastolic pressure or volume (4,5). Several clinical and epidemiological stu-

povećani tlak ili volumen na kraju dijastole (4,5). Nekoliko kliničkih i epidemioloških studija pokazalo je direktnu vezu između povećanja koncentracije plazme natrijuretskog peptida i smanjenih funkcija srčanih kljetaka, a posebno lijeve klijetke (6,7). Nedavno objavljene Smjernice za dijagnostiku i liječenje zatajivanja srca preporučaju korištenje BNP u dijagnostici zatajivanja srca (2,8). No, njegova je uloga u dijagnostici dijastoličkog zatajivanja srca još se uvijek sporna.

U ovom preglednom članku razmatra se dijagnostička vrijednost BNP u dijagnostici dijastoličkog zatajivanja srca.

Definicija dijastoličkog zatajivanja srca

Prema Smjernicama za dijagnostiku i liječenje zatajivanja srca koje je 2005. objavilo Europsko kardiološko društvo (8) dijagnostika primarnog dijastoličkog zatajivanja srca treba istovremeno zadovoljiti tri uvjeta: (i) postojanje znakova ili simptoma zatajivanja srca, (ii) evidentiranje poremećaja opuštanju lijeve klijetke, dijastolička rastezljivost odnosno krutost i (iii) očuvana sistolička funkcija lijeve klijetke.

Komponente dijastoličke disfunkcije lijeve klijetke uključuju poremećeno opuštanje i poremećenu dijastoličku komplijansu. Kateterizacija lijeve klijetke (održavanje odnosa tlaka i volumena, te mjerenje tlaka pod kojim se lijeva klijetka puni krvlju) predstavlja zlatni standard u dijagnostici disfunkcije lijeve klijetke. No, to je invazivna metoda te se stoga ne prakticira često u kliničkoj rutini. Umjesto nje, postoje razne neinvazivne dijagnostičke metode koje se primjenjuju za procjenu dijastoličke funkcije. Ultrazvuk je najčešće korištena metoda za procjenu dijastoličke disfunkcije. Brzina protoka krvi kroz plućnu venu i mitralni zalistak prikazana krivuljom transmitralnog protoka i dobivena pulsirajućom Doppler ehokardiografijom i brzina kružnog mitralnog toka krvi dobivena tkivnom Doppler metodom najkorisniji su parametri koji se koriste za procjenu dijastoličke disfunkcije (9-11). Kod bolesnika s dijastoličkom disfunkcijom opisana su tri poremećena tipa punjenja lijeve klijetke (12,13). Rani stadij dijastoličke disfunkcije naziva se *poremećeno opuštanje srčanog mišića*, napredni stadij dijastoličke disfunkcije naziva se *restriktivno punjenje*, a srednji tip između poremećenog opuštanja i restriktivnog punjenja definira se kao *pseudonormalno punjenje*. Svaki od ta tri tipa punjenja, poremećeno opuštanje srčanog mišića, pseudonormalno punjenje i restriktivno punjenje, predstavljaju blagu, umjerenu i jaku dijastoličku disfunkciju.

BNP

Srce izlučuje natrijuretski peptid kao homeostatski signal za održavanje stabilnog krvnog tlaka i volumena plazme te kako bi se spriječilo zadržavanje viška soli i vode. At-

dies have demonstrated a direct relationship between increasing plasma concentrations of natriuretic peptides and decreasing cardiac, especially left ventricular functions (6,7). Recent heart failure guidelines recommend that BNP can be used in the diagnosis of HF (2,8), however it's role in the diagnosis of diastolic heart failure is contentious. In this review paper we discuss the diagnostic value of BNP in diastolic HF.

Definition of diastolic heart failure

According to the 2005 Heart Failure Guideline from European Society of Cardiology (8), a diagnosis of primary diastolic HF requires three conditions to be simultaneously satisfied: (i) presence of signs or symptoms of heart failure, (ii) evidence of abnormal left ventricular relaxation, diastolic distensibility, or diastolic stiffness and (iii) preserved left ventricular systolic function.

The components of left ventricular diastolic dysfunction include impaired relaxation and decreased diastolic compliance. Left ventricular catheterization (obtaining pressure/volume relationship and measuring left ventricular filling pressures) is the gold standard tool in the diagnosis of left ventricular dysfunction, but it is an invasive method and it is not practical in clinical routine. Instead, different noninvasive diagnostic tools are applied for the assessment of diastolic function. Echocardiography is the most frequently used method for the evaluation of diastolic dysfunction. The transmitral and pulmonary venous flow velocities obtained by pulsed wave Doppler echocardiography and mitral annular velocities by tissue Doppler imaging are the most useful parameters used for the assessment of diastolic dysfunction (9-11). Three abnormal filling patterns have been described in patients with diastolic dysfunction (12,13). An early stage of diastolic dysfunction is *impaired myocardial relaxation*, an advanced stage of diastolic dysfunction is called *restrictive filling pattern* and an intermediate pattern between impaired relaxation and restrictive filling patterns is defined as *pseudonormalized filling pattern*. The three filling patterns impaired relaxation, pseudonormalized filling and restrictive filling represent mild, moderate, and severe diastolic dysfunction respectively.

BNP

The heart secretes natriuretic peptides as a homeostatic signal to maintain stable blood pressure and plasma volume, and to prevent excess salt and water retention. Atrial natriuretic peptide (ANP) was initially identified from the atrial myocardium of rats (14). In 1988 a compound was isolated from pig brain that caused natriuretic and diuretic responses similar to ANP

Eroglu S. i sur.   BNP i dijastoličko zatajivanje srca

Eroglu S. et al.   BNP and diastolic heart failure

rijski natrijuretski peptid (engl. *atrial natriuretic peptide*, ANP) je prvotno identificiran na srcu štakora (14). 1988. je iz mozga svinje izoliran spoj koji je izazivao natrijuretski i diuretski odgovor sličan ANP-u (15). Iako su taj peptid nazvali moždanim natrijuretskim peptidom, primarna lokacija njegove sinteze jest klijetka srčanog mišića (16,17). Mišićne stanice srca izlučuju BNP prekursor koji se sintetizira u proBNP, koji se sastoji od 108 aminokiselina. Nakon što se izluči u klijetke, proBNP se cijepa na biološki aktivan C-terminalni dio (32 aminoliselinski aktivni hormonski BNP) i biološki neaktivan N-terminalni dio [76 aminoliselinski N-terminalni proBNP (NT-proBNP)]. Genska ekspresija BNP može se jako brzo povećati kao odgovor na određeni stimulans (18). Identificirana su tri receptora natrijuretskog peptida (NPR-A, NPR-B i NPR-C) (19). Vezanje natrijuretskih peptida na receptore A i B na površini ciljnih stanica vodi ka stvaranju drugog glasnika cGMP (engl. *cyclic guanosine monophosphate*; ciklički gvanozin monofosfat) koji posreduje u većini bioloških učinaka natrijuretskih peptida (19). BNP se prvenstveno veže na NPR-A receptore. NPR-C je receptor putem kojeg se BNP uklanja iz plazme. Slabije vezanje NPR-C-a na BNP doprinosi duljem poluživotu u plazmi BNP u usporedbi s ANP kod ljudi (19). Natrijuretski su peptidi također inaktivirani neutralnom endopeptidazom, cink metalopeptidazom koji se nalazi na površini endotelnih stanica, glatkih mišićnih stanica, srčanih mišićnih stanica, bubrežnog epitelija i fibroblasta (20).

Natrijuretski peptidi imaju nekoliko funkcija:

- smirivanje simpatičnog živčanog sustava (21) i renin-angiotenzin-aldosteronskog sustava (22,23);
- omogućavanje izlučivanja natrija mokraćom i mokrenja preko aferentnih i eferentnih hemodinamičnih mehanizama bubrega i distalnih tubula (24);
- smanjenje periferne krvožilne rezistencije (25); i
- povećanje opuštanja glatkih mišića (25);
- usmjeravanje opuštajućih svojstava u srčani mišić (26);
- antiproliferativno i antifibrotičko djelovanje na krvožilno tkivo (27, 28); dakle, sprečavanje rasta i hipertrofije (dilatacije) srčanog mišića te djelovanje protivno mitogenezi koja uzrokuje histološke promjene u stjenci klijetke.

BNP i dijastoličko zatajivanje srca

Doprinosi neurohormona razvoju kliničke manifestacije dijastoličke disfunkcije su kompleksni. Razlika između kliničke stabilnosti i dekompenzacije je stvar ravnoteže između aktivnosti na razini renin-angiotenzin-aldosteronskog sustava, aktivnosti simpatičnog živčanog sustava, endotelina i arginin-vazopresin regulacijskih mehanizama te kontraregulatornih hormona ANP, BNP i natrijuretskog peptida C tipa (29). ANP i BNP smatraju se kontraregulator-

(15). Although this peptide was called brain natriuretic peptide, the primary site of BNP synthesis is ventricular myocardium (16,17). Cardiac myocytes secrete a BNP precursor that is synthesized into proBNP, which consists of 108 amino acids. After it is secreted into the ventricles, proBNP is cleaved into the biologically active C-terminal portion (32 aminoacid active hormone-BNP) and the biologically inactive N-terminal portion [76 aminoacid N-terminal proBNP (NT-proBNP)]. BNP gene expression can increase very rapidly in response to an appropriate stimulus (18). Three natriuretic peptide receptors have been identified (NPR-A, NPR-B, and NPR-C) (19). Binding of natriuretic peptides to the A and B receptors on the surface of target cells leads to generation of the second messenger cGMP (cyclic guanosine monophosphate), which mediates most of the biological effects of the natriuretic peptides (19). BNP binds preferentially to NPR-A receptors. NPR-C is a clearance receptor for BNP. Lower affinity of NPR-C for BNP contributes to a longer plasma half-life of BNP compared with ANP in human beings (19). Natriuretic peptides are also inactivated by neutral endopeptidase, a zinc metallopeptidase that is present on the surface of endothelial cells, smooth-muscle cells, cardiac myocytes, renal epithelium, and fibroblasts (20).

Natriuretic peptides have several actions:

- down-regulating the sympathetic nervous system (SNS) (21) and the renin angiotensin-aldosterone (RAAS) system (22,23);
- facilitating natriuresis and diuresis through the afferent and efferent hemodynamic mechanisms of the kidney and distal tubules (24);
- decreasing peripheral vascular resistance (25); and
- increasing smooth muscle relaxation (25);
- direct lusitropic (relaxing) properties in the myocardium (26);
- antiproliferative and antifibrotic effects in vascular tissues (27,28), therefore inhibiting cardiac growth and hypertrophy, counteracting the mitogenesis that causes ventricular remodelling.

BNP and diastolic heart failure

Neurohormonal contributions to the development of clinical manifestations of diastolic dysfunction are complex. The difference between clinical stability and decompensation is a balancing act between the actions of the RAAS axis, SNS activity, endothelin, and arginine vasopressin regulatory systems, and the counterregulatory hormones ANP, BNP, and C-type natriuretic peptide (29). ANP and BNP are considered counter-regulatory to the RAAS through their actions of vasodilation and natriuresis. BNP found in high concentrations in the ventricles, has been studied extensively as a serologic marker of volume overload and increased LV pressures (30).

nima renin-angiotenzin-aldosteronskog sustava zbog dje-lovanja na proširenje krvnih žila i izlučivanje natrija mokra-ćom. BNP pronađen u visokim koncentracijama u klijetka-ma opsežno se istraživao kao serološki marker prevelikog volumena i povećanog tlaka lijeve klijetke (30).

U zadnje vrijeme sakupljeni podaci pokazali su da su se koncentracije BNP povećavale kod zatajivanja srca, što je od velike važnosti za diferencijalnu dijagnostiku dispneje. Maisel i sur. (31) su zaključili temeljem mjerenja koncentra-cije BNP u plazmi kod 1586 bolesnika s dijagnozom akut-ne dispneje da se vrijednost izmjerene koncentracije BNP u plazmi može koristiti za razlikovanje između dispneje uz-rokovane zatajivanjem srca i one plućnog uzroka. Granič-na koncentracija BNP u plazmi od 100 pg/mL potvrdila je dijagnozu zatajivanja srca s osjetljivosti 90%, specifičnosti 76%, pozitivnom predikativnom vrijednosti 79%, negativ-nom predikativnom vrijednosti 89% te dijagnostičkom točnosti 83%. BNP se posebno koristi kod isključivanje di-jagnoze zatajivanja srca; na graničnoj vrijednosti BNP od 50 pg/mL, negativna prediktivna vrijednost bila je 96%.

U nekim se studijama ispitivalo povećanje koncentracije BNP kod različitih tipova zatajivanja srca. Sistolička i dijas-tolička disfunkcija lijeve klijetke povećavaju koncentraciju BNP u plazmi u različitim razmjerima. Wei i sur. (32) istraži-li su koncentracije BNP kod 149 bolesnika sa dijagnozom zatajivanja srca i pokazali su da je sistolička disfunkcija li-jeve klijetke povezana s višom koncentracijom BNP u plaz-mi nego dijastolička disfunkcija lijeve klijetke (srednja vri-jednost koncentracije BNP-a kod dijastoličke disfunkcije lijeve klijetke bila je 115 ± 80 pg/mL; a kod sistoličke dis-funkcije lijeve klijetke 516 ± 445 pg/mL (P < 0,05). Jedna druga studija (33) pokazuje da su koncentracije BNP više kod bolesnika sa sistoličkom disfunkcijom, nego kod onih s izoliranom dijastoličkom disfunkcijom, a najveća kod onih s obje, sistoličkom i dijastoličkom disfunkcijom. U meta-analizi 20 studija koje su vrednovale dijagnostičku točnost natrijuretskog peptida u dijagnostici zatajivanja srca, upotreba granične vrijednosti BNP ili NT-proBNP od 15 pmol/L (BNP 52 pg/mL i NT-proBNP 127 pg/mL) osigu-rava visoku osjetljivost, a niže koncentracije BNP, odnos-no one ispod te vrijednosti, isključuju dijagnozu zatajiva-nja srca u bolesnika sa sumnjom na tu bolest (34). Kod dvije od studija u toj meta-analizi koje su ehokardiograf-skim kriterijima za dijagnozu sistoličkog i dijastoličkog zatajivanja srca mjerile BNP, dijagnostički je omjer rizika (engl. *diagnostic odd ratio*, DOR) (37,7; 95% CI =5,9-237,2) bio veći nego u studijama koje su mjerile samo sistoličku funkciju (34).

U nekoliko studija se ispitivala uloga BNP u dijagnostici izoliranog dijastoličkog zatajivanja srca. Lubien i sur. (35) su pokazali da se pomoću određivanja koncentracija BNP, mogu predvidjeti dijastolički poremećaji kod bolesnika s normalnom sistoličkom funkcijom. U toj su studiji bolesni-ci s poremećenom dijastoličkom funkcijom imali srednju

Accumulating recent data showed that BNP levels were increased in heart failure and it is especially important in the differential diagnosis of dyspnea. Maisel et al (31) as-sessed value of rapid bedside measurements of plasma BNP in distinguishing between heart failure and a pulmo-nary a cause of dyspnea in 1586 patients presenting with acute dyspnea. A cut-off plasma BNP value of 100 pg /mL diagnosed heart failure with a sensitivity, specificity, posi-tive predictive value, negative predictive value and diag-nostic accuracy of 90%, 76%, 79%, 89% and 83%, respecti-vely. BNP was especially useful for ruling out heart failure; at a BNP threshold of 50 pg/mL, the negative predictive value was 96%.

The degree of BNP increase was examined in different ty-pes of the heart failure in some studies. Left ventricular systolic and diastolic dysfunction increase plasma BNP concentrations to a different extent. Wei et al (32) inves-tigated BNP levels in 149 heart failure patients and they showed that left ventricular systolic dysfunction is asso-ciated with a higher level of plasma BNP than left ventri-cular diastolic dysfunction (mean BNP level in left ventri-cular diastolic dysfunction was 115 ± 80 pg/mL; in left ventricular systolic dysfunction was 516 ± 445 pg/ml (P < 0.05). In another study (33), the concentrations of BNP are higher in patients with systolic dysfunction than in those with isolated diastolic dysfunction, and highest in those with both systolic and diastolic dysfunction.

In a meta-analysis of 20 studies where the diagnostic ac-curacy of natriuretic peptides for heart failure was evalua-ted, the use of a cut-off value for BNP or NT-proBNP of 15 pmol/L (52 pg/mL and 127 pg/mL, respectively) achieves high sensitivity, and BNP values below this exclude hea-rt failure in patients in whom disease is suspected (34). Two of the studies in this meta-analysis that measured BNP against echocardiographic criteria for both systolic and diastolic heart failure, the diagnostic odd ratio (DOR) (37.7; 95% CI = 5.9-237.2) was greater than in studies that measured only systolic function (34).

The role of BNP in the diagnosis of isolated diastolic heart failure has been examined in several studies. Lubien et al (35) showed that BNP levels could predict diastolic abnor-malities in patients with normal systolic function. In this study the patients diagnosed with abnormal diastolic fun-ction had a mean BNP concentration of 286 ± 31 pg/mL, whereas the control subjects had a mean BNP concentra-tion of 33 ± 3 pg/mL. A BNP value of 62 pg/mL had a sensi-tivity of 85%, a specificity of 83%, and an accuracy of 84% for detecting diastolic dysfunction. In a meta-analysis, th-ree studies that measured BNP in diastolic heart failure had 28.8; (95 % CI = 2.66-300.5) DOR (34).

vrijednost koncentracije BNP od 286 ± 31 pg/mL, dok je koncentracija kod kontrolnih ispitanika iznosila 33 ± 3 pg/mL. Koncentracija BNP od 62 pg/mL imala je osjetljivost 85%, specifičnost 83% i dijagnostičku točnost 84% u korist postavljanja dijagnoze dijastoličke disfunkcije. U meta-analizi, tri studije koje su mjerile BNP kod dijastoličkog zatajivanja srca imale su DOR od 28,8 (95 % CI = 2,66-300,5) (34).

Razlike koncentracija BNP prema stupnju dijastoličke disfunkcije

Lubien i sur. (35) su otkrili da su se koncentracije BNP razlikovale u podgrupama dijastoličke disfunkcije, no sve su podgrupe imale višu koncentraciju BNP nego kontrolni ispitanici. Bolesnici s pokazateljima restriktivnog punjenja lijeve klijetke na ultrazvuku imali su najviše koncentracije BNP (408 ± 66 pg/mL). Yu i sur. (36) su prikazali da su se koncentracije BNP povećale kod bolesnika s pseudonormalnim ili restriktivnim tipom punjenja. Te su studije otkrile da su bolesnici s pseudonormalnim tipom punjenja imali više koncentracije BNP od onih s poremećenim opuštanjem srčanog mišića. Koncentracije BNP se povećavaju prema stadiju/tipu dijastoličke disfunkcije. U ranom stadiju dijastoličke disfunkcije, kod poremećaja opuštanja, koncentracije BNP blago se povećavaju; u srednjem stadiju, pseudonormalnom tipu punjenja, zabilježene su umjereno povećane koncentracije BNP; dok su u naprednom stadiju dijastoličke disfunkcije, restriktivnom punjenju lijeve klijetke, koncentracije BNP-a značajno povišene.

Bolesnici sa simptomima su u svim dijastoličkim tipovima punjenja imali povišene koncentracije BNP. Kao skupina, bolesnici s dijastoličkom disfunkcijom i simptomima su imali više koncentracije BNP nego oni bolesnici s asimptomatičnom dijastoličkom disfunkcijom (35). Iako je kod sistoličkog zatajivanja srca BNP u uzajamnoj vezi s volumenom, veličinom i istisnom frakcijom lijeve klijetke, kod dijastoličkog zatajivanja srca s očuvanom istisnom frakcijom lijeve klijetke on nije povezan s veličinom, volumenom i masom lijeve klijetke. Yamaguchi i suradnici (37) su našli da su unatoč sličnoj raspodijeli mase i veličine lijeve klijetke, koncentracije BNP kod bolesnika s dijastoličkim zatajivanjem srca bile više nego kod kontrolnih ispitanika (149 ± 38 prema 31 ± 5 pg/mL, P < 0,01). Naveli su da bi povećanje BNP mogao biti znak raspoznavanja bolesnika koji već imaju ili su u rizičnoj grupi da obole od dijastoličkog zatajivanja srca među ispitanicima s očuvanom sistoličkom funkcijom neovisno o hipertrofiji lijeve klijetke. Pokazano je da koncentracije BNP kod bolesnika s normalnom sistoličkom funkcijom lijeve klijetke ne ovise o masi lijeve klijetke, srčanom indeksu i srčanoj frekvenciji (37,38).

Koncentracije BNP mogu povremeno biti unutar granica referentnog raspona kod bolesnika s dijastoličkom disfunkcijom. Mogu se nalaziti unutar granica referentnog ras-

Differences of BNP concentration according to stage of diastolic dysfunction

Lubien et al (35) revealed that BNP concentrations were different in subgroups of diastolic dysfunction but all subgroups had higher BNP levels than control subjects. Patients with restrictive filling patterns on echocardiography had the highest BNP levels (408 ± 66 pg/mL). Yu et al (36) showed that BNP concentrations were increased in patients with pseudonormalized or restrictive filling pattern. These studies revealed that patients with the pseudonormalized filling pattern had higher BNP concentrations than patients with impaired relaxation. BNP concentrations increase according to the stage/type of diastolic dysfunction. In the early stage of diastolic dysfunction, impaired myocardial relaxation, BNP levels mildly increase; in an intermediate stage, pseudonormalized filling pattern, moderately increased BNP concentrations are noted; and in an advanced stage of diastolic dysfunction, restrictive filling pattern, BNP concentrations are markedly increased.

Patients with symptoms had higher BNP levels in all diastolic filling patterns. As a group, patients with diastolic dysfunction and symptoms had higher BNP levels than those patients with asymptomatic diastolic dysfunction (35). Although BNP correlate with LV volume, size and EF in systolic heart failure, it is not associated with LV size, volume and mass in diastolic heart failure with preserved left ventricular EF. Yamaguchi and coauthors (37) found that, despite a similar distribution of LV mass and size, concentrations of BNP were higher in patients with diastolic HF than in the controls (149 ± 38 vs. 31 ± 5 pg/mL, P < 0.01). They stated that an elevation of BNP may be a hallmark of patients with or at risk of diastolic HF among subjects with preserved systolic function independent of LV hypertrophy. It has been shown that BNP levels in patients with normal left ventricular systolic function are not affected by left ventricular mass, cardiac output, or cardiac index (37,38).

Occasionally BNP levels might be in normal range in patients with diastolic dysfunction. It can be normal in asymptomatic patients with a mild degree of diastolic dysfunction, impaired relaxation. Mottram and colleagues (38) have demonstrated that BNP concentrations are higher in patients having diastolic dysfunction than they are in those with normal diastolic function. In that study, the authors also found that BNP concentrations were higher in patients with pseudonormalized pattern than they were in those with abnormal relaxation pattern. In our study we evaluated BNP levels and functional capacity determined by cardiopulmonary exercise test in patients with isolated diastolic dysfunction. We detected a correlation between BNP concentrations and functional capacity (39). However, since our patients had mostly

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pona i kod asimptomatičnih bolesnika s blagim stupnjem dijastoličke disfunkcije, poremećenim opuštanjem. Mottram i suradnici (38) su pokazali da su koncentracije BNP više kod bolesnika koji imaju dijastoličku disfunkciju nego kod onih s normalnom dijastoličkom funkcijom. U toj studiji autori su također pronašli da su koncentracije BNP bile više kod bolesnika s pseudonormalnim tipom punjenja nego kod onih s poremećenim tipom punjenja. U našoj smo studiji vrednovali koncentracije BNP i funkcionalni kapacitet dobiven testom opterećenja (kardiopulmonarnim testom) kod bolesnika s izoliranom dijastoličkom disfunkcijom. Primijetili smo uzajamnu zavisnost između koncentracija BNP i funkcionalnog kapaciteta (39). No, budući da su naši bolesnici bolovali u većini slučajeva od blage dijastoličke disfunkcije, poremećaja u opuštanju srčanog mišića, srednje vrijednosti koncentracija BNP bile su unutar granica referentnog raspona.

U jednom svom preglednom članku Dahlströrm (40) je objavio da natrijuretski peptidi nisu aktivirani kod bolesnika koji imaju dijastoličku disfunkciju u obliku odgođene relaksacije (opuštanja). Stoga se ne čini adekvatnim u kliničkoj rutini mjeriti koncentraciju BNP ili NT-proBNP u svrhu otkrivanja bolesnika s blagim poremećajima u opuštanju. Optimalna granična vrijednost za dijastoličko zatajivanje srca još je nejasna. BNP ima ulogu u otkrivanju bolesnika s dijastoličkom disfunkcijom, posebno kod onih bolesnika s restriktivnim ili pseudonormalnim tipom punjenja. Bolesnici s poremećajem opuštanja i blagim simptomima ili oni koji su asimptomatični mogu imati normalne koncentracije BNP što ukazuje na normalan ili samo blago povišen tlak punjenja lijeve klijetke. Stoga se niske koncentracije ne mogu koristiti u svrhu isključivanja dijagnoze dijastoličke disfunkcije. Međutim, ako se pojave visoke koncentracije BNP onda se trebaju napraviti daljnje pretrage ultrazvukom kako bi se potvrdila dijagnoza poremećaja rada srca.

NT-proBNP (engl. *N-Terminal pro B-type natriuretic peptide*)

NT-proBNP je biološki neaktivan fragment. Oslobađaju ga prvenstveno klijetke kao odgovor na rastezanje, slično kao i BNP. NT-proBNP cirkulira u većoj koncentraciji plazme i ima dulji poluživot u usporedbi s BNP (41). Isto kao i BNP, može se koristiti u dijagnostici zatajivanja srca (42). Otkriveno je da je NT-proBNP povišen kod izolirane dijastoličke disfunkcije i da može biti koristan za otkrivanje svih stupnjeva dijastoličke disfunkcije. (43). Koncentracije NT-proBNP se znatno povećavaju prema jačini sveukupne dijastoličke disfunkcije, pokazujući pritom karakteristike slične BNP (43). U meta-analizi su sakupljene procjene osjetljivosti i specifičnosti bile iste za BNP kao i za NT-proBNP. BNP i NT-proBNP imaju vrlo slične dijagnostičke karakteristike te se mogu koristiti u svrhu isključivanja di-

mild diastolic dysfunction, impaired relaxation pattern, the mean BNP concentrations were in normal range.

In a review article, Dahlströrm (40) stated that natriuretic peptides are not activated in patients having diastolic dysfunction in the form of delayed relaxation. Thus, it seems not appropriate to measure BNP or NT-proBNP level in clinical routine to detect patients with mild relaxation abnormalities.

The optimal cut-off value for a diastolic heart failure diagnosis is unclear. The BNP has a role in detecting patients with diastolic dysfunction especially in those patients having a restrictive or pseudonormalized filling pattern. Patients with relaxation abnormalities and mild symptoms or who are asymptomatic may have normal BNP levels, indicating normal or only slightly elevated left ventricular filling pressures. Thus, low levels cannot be used to rule out diagnosis of diastolic dysfunction. However, if there are high concentrations of the BNP, there is a need for further investigation with echocardiography to verify the diagnosis of abnormal cardiac function.

NT-proBNP (*N-Terminal pro B-type natriuretic peptide*)

NT-proBNP is a biologically inactive fragment. NT-proBNP is released predominantly by the ventricles in response to stretch, similar to BNP. NT-proBNP circulated at higher plasma concentrations and has a longer half-life compared with BNP (41). It may be used for the diagnosis of heart failure as BNP (42). NT-proBNP was found to be high in isolated diastolic dysfunction and it could be useful for the detection of all degrees of diastolic dysfunction (43). NT-proBNP levels are increased significantly according to the severity of overall diastolic dysfunction, displaying a pattern similar to BNP (43). In a meta-analysis the pooled estimates of sensitivity and specificity were the same for the BNP studies as for the NT-proBNP studies. BNP and NT-proBNP have very similar diagnostic performance characteristics and can be used to rule out heart failure. However, there is no easily identifiable optimum cut point value for each peptide (44). The other meta-analysis both BNP and NT-proBNP assays have a high degree of diagnostic accuracy and clinical relevance for both acute and chronic heart failure (45).

Influences on BNP and NT-proBNP concentrations

The optimal cut-off value of BNP and NT-ProBNP for the diagnosis of diastolic heart failure is unclear. It may relate some factors. The most important factors the cut-off values of BNP and NT-proBNP are method-dependent. Hammerer- Lercher et al (46) pointed out that the performance of BNP for the diagnosis of systolic or diastolic left

jagnoze zatajivanja srca. Međutim ne postoji lako odrediva optimalna granična vrijednost za svaki peptid (44). Druge meta-analize oba testa, i BNP testa i NT-proBNP testa imaju visok stupanj dijagnostičke točnosti i kliničkog značaja za akutan i kroničan oblik zatajivanja srca (45).

Utjecaji na koncentracije BNP i NT-proBNP

Optimalna granična vrijednost BNP i NT-proBNP u dijagnostici dijastoličkog zatajivanja srca je nejasna. Ona može biti povezana s nekim čimbenicima. Najbitniji čimbenici graničnih vrijednosti BNP i NT-proBNP ovise o metodi. Hammer-Lercher i sur. (46) su istaknuli da na učinak BNP u dijagnostici sistoličke ili dijastoličke disfunkcije lijeve klijetke ne utječe test koji se koristi, dok je učinak NT-proBNP u dijagnozi izolirane dijastoličke disfunkcije lijeve klijetke ovisan o testu (46). Pronašli su da oba BNP testa (od proizvođača Triage i Shionoria) i oba NT-proBNP testa (od proizvođača Biomedica i Roche) djelovala jednako dobro za postavljanje dijagnoze sistoličke disfunkcije lijeve klijetke unatoč slaboj usklađenosti između testova za NT-proBNP (46). Kod bolesnika s izoliranom dijastoličkom disfunkcijom lijeve klijetke dijagnostički učinak Triage BNP testa znatno je bolji od učinka Biomedica NT-proBNP testa. Nadalje, učinak Biomedica NT-proBNP testa znatno je lošiji od učinka Roche NT-proBNP testa u dijagnostici izolirane dijastoličke disfunkcije lijeve klijetke. U drugim je studijama prikazano da Triage BNP test u usporedbi sa Shionoria testom daje dosljedno više vrijednosti i ta magnituda razlike rezultata raste s većom koncentracijom peptida (i jačinom zatajivanja srca) (46,47). Test tvrtke Biomedica pokazuje znatno više vrijednosti u usporedbi s Elecsys metodom (tvrtka Roche) te sugerira da su potrebne više granične vrijednosti kako bi bile usporedive (46,48).

Raymond i sur. (49) su pokazali ostale čimbenike za određivanje granične vrijednosti za dijagnostiku zatajivanja srca. Otkrili su da je svaki od sljedećih čimbenika: ženski spol, viša dob, pojačana dispneja, šećerna bolest, bolest srčanih zalistaka, sniženje srčane frekvencije, istisna frakcija lijeve klijetke < 45%, patološki EKG, visoka koncentracija kreatinina u plazmi, niska koncentracija HbA1c u plazmi i visoka koncentracija albumina u mokraći, pojedinačno povezani s visokom koncentracijom NT-proBNP u plazmi. Neki lijekovi koji se koriste u liječenju zatajivanja srca mogu djelovati na koncentraciju natrija u mokraći. Diuretici kao npr. spironolakton, inhibitor angiotenzin-konvertaze, blokator receptora angiotenzina II smanjuju koncentracije natrijuretskih peptida (50). Stoga će kod mnogih bolesnika s kroničnim stabilnim zatajivanjem srca koncentracije BNP biti u granicama referentnog raspona. Međutim čini se da digoksin i neki beta-blokatori povećavaju koncentracije natrijuretskih peptida (50-52).

Vježbanje uzrokuje lagano povećanje koncentracije BNP koje se mogu otkriti u kratkom roku (nakon jednog sata

ventricular dysfunction is not affected by the assay used, whereas the performance of NT-proBNP for the diagnosis of isolated diastolic left ventricular dysfunction is assay dependent (46). They found that both BNP assays (Triage and Shionoria) and both NT-proBNP assays (Biomedica and Roche) performed equally well for the diagnosis of systolic left ventricle dysfunction despite the poor agreement between NT-proBNP assays (46). In patients with isolated diastolic left ventricular dysfunction, the diagnostic performance of the Triage BNP was significantly better than that of Biomedica NT-proBNP. Furthermore, the performance of the Biomedica NT-proBNP assay was significantly worse than that of the Roche NT-proBNP assay for diagnosis of isolated diastolic left ventricular dysfunction. In other studies the Triage BNP assay when compared to the Shionoria assay gives consistently higher values and the magnitude of difference increases with concentration (and severity of heart failure) of peptide (46,47). The Biomedica method shows considerably higher values compared to the Elecsys method (Roche) suggesting that higher cut-off values are needed to be comparable (46, 48).

Other factors in determining a cut point value for the diagnosis of HF were demonstrated by Raymond et al (49). They found that female sex, age, increasing dyspnea, diabetes mellitus, valvular heart disease, low heart rate, left ventricular ejection fraction < 45%, abnormal ECG, high plasma creatinine, low plasma HbA1c, and high urine albumin were each independently associated with a high plasma NT-proBNP level.

Some medications used to treat heart failure might affect natriuretic concentrations. Diuretics such as spironolactone, angiotensin-converting enzyme inhibitors, angiotensin-II receptor blockers reduce natriuretic peptide concentrations (50). Therefore, many patients with chronic stable heart failure will have BNP levels in the normal diagnostic range. However, digoxin and some beta blockers appear to increase natriuretic peptide concentrations (50-52).

Exercise causes a slight increase in BNP levels which are detectable at short-term (one hour after exercise) (53) (i.e., increase of 0.9 percent in patients without heart failure, 3.8 percent in patients with New York Heart Association [NYHA] class I or II heart failure, and 15 percent in patients with NYHA class III to IV heart failure) (54).

No circadian variation has been reported when BNP is measured every three hours for 24 hours (55) and there is less hourly variation with BNP than with ANP (56).

Conclusion

BNP concentrations increase in diastolic HF but it is typically lower than that in systolic HF. BNP concentrations correlate with the stage of diastolic dysfunction. Concen-

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vježbe) (53) (npr. povećanje od 0,9 % kod bolesnika bez zatajivanja srca, 3,8% kod bolesnika sa zatajivanjem srca NYHA (engl. *New York Heart Assossiation*) stadija I ili II i 15% kod bolesnika sa zatajivanjem srca NYHA stadija III ili IV) (54). Pri mjerenjima BNP svaka 3 sata unutar perioda od 24 sata, nije bilo dnevne varijacije (55) i kod BNP postoji manja varijacija po satu nego kod ANP (56).

Zaključak

Povećanje koncentracije BNP kod dijastoličkog zatajivanja srca je obično niže nego kod sistoličkog zatajivanja srca. Koncentracije BNP u uzajamnoj su vezi sa stadijem dijastoličke disfunkcije. Koncentracija može biti povišena kod bolesnika sa simptomima poremećenog opuštanja srčanog mišića, a najviša je kod bolesnika s restriktivnim tipom punjenja. Koncentracije BNP kod bolesnika s dijastoličkom disfunkcijom rastu kako oni postaju simptomatični. Ponekad kod bolesnika s poremećenim opuštanjem koncentracija BNP može biti unutar granica referentnog raspona. Stoga se niske koncentracije BNP ne bi trebale koristiti za isključivanje dijagnoze dijastoličke disfunkcije. Međutim ako se pojavi visoka koncentracija BNP potrebno je napraviti daljnje pretrage kako bi se potvrdila dijagnoza poremećenog rada srca. Optimalna granična vrijednost za dijagnostiku dijastoličkog zatajivanja srca nije precizno definirana, zbog činjenice da je učinak BNP i NT-proBNP za dijagnostiku izolirane dijastoličke disfunkcije lijeve klijetke ovisan o testu.

trations might be raised among patients with evidence of impaired relaxation and highest among those with a restrictive filling pattern. BNP concentrations increase in patients with diastolic dysfunction as they become symptomatic. Sometimes in impaired relaxation groups it might be in normal range. Therefore low levels should not be used as a rule out the diagnosis of diastolic dysfunction. However, if there are high concentrations of the BNP there is a need for further investigation to verify the diagnosis of abnormal cardiac function. The optimal cut-off value for the diagnosis of diastolic heart failure is not defined accurately because of the performance of BNP and NT-proBNP for the diagnosis of isolated diastolic left ventricular dysfunction is assay dependent.

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