Razumijevanje zatajivanja srca: evolucija shvaćanja i liječenja

Understanding Heart Failure: Evolution of Concepts and Treatments

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SAŽETAK: Stariji se kardiolozi mogu prisjetiti evolucije poimanja patofiziologije zatajivanja srca (HF) i pristupa liječenju tijekom profesionalne karijere. Milton Packer je nedavno napredak koncepcije HF-a sažeo u četiri stadija: 1) kardiorenalni model (od 40-ih do kraja 60-ih godina prošloga stoljeća), 2) kardiocirkulacijski model ili hemodinamska hipoteza (70-e i 80-e godine 20. st.), 3) neurohormonalni model (od 90-ih godina 20. st. donedavno) i 4) najnoviji model staničnog opterećenja. Kardiorenalni se model oslanjao na liječenje digitalisom i diureticima. Vazodilatatori i pozitivni inotropi pobudili su nade u vrijeme dominacije hemodinamske hipoteze, ali nisu opravdali očekivanja. Tek je neurohormonalni pristup s inhibitornima renin-angiotenzin-aldosteronskog sustava i beta-blokatorima kao djelatnim lijekovima postigao trajno poboljšanje najvažnijih kliničkih ishoda, uključujući smrtnost. Takvo je liječenje, međutim, bilo neučinkovito u zatajivanju srca s očuvanom ejekcijskom frakcijom (HFpEF), tj. u polovice svih bolesnika s HF-om. Sretan splet okolnosti otkrio je da su inhibitori suprijenosnika natrija-glukoze 2 (SGLT2 inhibitori), prvotno uvedeni kao antidijabetički lijekovi, korisni i za kardiovaskularni sustav. Ta je spoznaja potaknula klinička istraživanja kojima su dokazani korisni učinci na ishode liječenja ne samo zatajivanja srca s reduciranom ejekcijskom frakcijom nego i HFpEF. Kada se misterij načina SGLT2 inhibitora počeo razotkrivati, najavljen je model staničnog opterećenja u HF-u. Pregled je usredotočen na povijesne i nove patofiziološke koncepcije HF-a, zajedno s odgovarajućim lijekovima, ali su spomenuti i nefarmakološki načini liječenja. Na kraju se raspravlja o izgledima za daljnji napredak razumijevanja i liječenja HF-a.

SUMMARY: Senior cardiologists can recall the evolution of cardiologists' views on heart failure (HF) pathophysiology and treatment approaches during their professional career. Milton Packer has recently formulated the progress of HF concepts in four stages: 1) the cardiorenal model (1940s through the 1960s), 2) the cardiocirculatory model or hemodynamic hypothesis (1970s and 1980s), 3) the neurohormonal model (from 1990s up to recently), and 4) the recent cellular stress model. The cardiorenal model relied on digitalis and diuretics. Vasodilators and positive inotropes were viewed with hope at the time of the prevalence of the hemodynamic hypothesis, but did not meet expectations. Only the neurohormonal model with renin-angiotensin-aldosterone system inhibitors and beta-blockers as acting drugs provided permanent improvement in substantial clinical outcomes, including death rates. However, those treatments were ineffective in heart failure with preserved ejection fraction (HFpEF), comprising half of all patients with HF. The serendipitous discovery that sodium-glucose cotransporter-2 (SGLT2) inhibitors, first introduced as antidiabetic drugs, have beneficial cardiac effects, led to clinical trials which proved substantial outcome benefits not only in heart failure with reduced ejection fraction but also in HFpEF. As the mystery shrouding the mechanisms of sodium-glucose cotransporter 2 inhibitors actions began to be unraveled, the cellular stress model of HF was introduced. This review is focused on historical and recent HF pathophysiological concepts, along with the drugs associated with them, but non-pharmacological treatments are also addressed. Finally, the prospects for advancements in the understanding and treatment of HF are also discussed.

KLJUČNE RIJEČI: zatajivanje srca, neurohormonalna inhibicija, stanično opterećenje.

KEYWORDS: heart failure, neurohormonal inhibition, cellular stress.

CITATION: Cardiol Croat. 2024;19(7-8):251-69. | https://doi.org/10.15836/ccar2024.251

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RECEIVED: April 30, 2024

UPDATED: May 24, 2024

ACCEPTED: June 3, 2024

TO CITE THIS ARTICLE: Šmalcelj A. Understanding Heart Failure: Evolution of Concepts and Treatments. Cardiol Croat. 2024;19(7-8):251-69. | https://doi.org/10.15836/ccar2024.251

TO LINK TO THIS ARTICLE: https://doi.org/10.15836/ccar2024.251

Povijesna pozadina

Epohalno otkriće krvotoka sa srcem kao pokretačem Williama Harveyja (1628.) postavilo je temelj

Historical background

William Harvey's epochal discovery of blood circulation driven by a heart pump in 1628 provided

koncepcije zatajivanja srca (HF). Drevni grčki i rimski liječnici pripisivali su edem, anasarku i dispneju drugim razlozima, a ne bolesti srca, vjerujući da pleuralni izljevi potječu iz mozga, a da srce raspodjeljuje toplinu i duh života. Povezivanje bolesti srca s hemodinamskim i kliničkim poremećajima nakon Harveyjeva je otkrića potrajalo. G. M. Lancisi (1654. – 1720.) uočio je da proširenje slabi srce. J. N. Corvisart pisao je 1806. da proširenje srca povezano s valvulnom regurgitacijom navješćuje HF i loš ishod. Godine1982. W. Osler gledao je na hipertrofiju srca kao na korak prema HF-u („slomljena kompenzacija"). Ti i mnogi drugi liječnici, glasoviti, ili slabije poznati, u tančine su opisali kliničku sliku i tijek HF-a[1-3].

U početku su patofiziološka shvaćanja bila krajnje jednostavna, svodeći HF na slabost samoga srca kao uzroka smanjenja minutnog volumena i zadržavanja izvanstanične tekućine koja se nakuplja u plućima i tkivima. Liječenje je bilo iskustveno i neučinkovito. Prolazno se olakšanje postizalo prilagodbom načina života. Puštanje krvi i pijavice primjenjivali su se stoljećima. Southeyeve cjevčice za drenažu edema odavno su zaboravljene. Među raznim biljnim pripravcima jedino su preparati digitalisa (naprstka) bili zgoditak. Od uvođenja u medicinsku uporabu 1785. po W. Witheringu, digitalis je bio oslonac liječenja HF-a tijekom 200 godina, sve donedavno[4–9].

Najava novoga vremena: pripovijest o diureticima

Pronalazak učinkovitih diuretika kasnih 50-ih godina prošloga stoljeća navijestio je novo doba modernoga farmakološkog liječenja HF-a. Do 1957. jedini diuretici uporabljivani pri HF-u bili su intravenski ili intramuskularni živini diuretici, toksični i nespretni za uporabu. Otkriće modernih diuretika posrećilo se pri proučavanju nuspojava sulfonamida. Godine 1937./38. istraživanje sulfonamida otkrilo je njihove diuretske učinke. Razvoj inhibitora karboanhidraze acetazolamida unaprijedio je 1945. razumijevanje mehanizama diureze u bubrežnim tubulima. Među mnogim spojevima sintetiziranima u potrazi za učinkovitim inhibitorima karboanhidraze istraživanje se spotaknulo na klorotiazid koji ne samo da inhibira karboanhidrazu nego i sustav kotransporta natrijeva klorida. Godine 1959. klorotiazid je uveden kao prvi uporabljiv peroralni diuretik. Još se naveliko uporabljuje, ali mnogo više kao antihipertenziv nego kao lijek za liječenje HF-a[10–12].

Tiazidi i njima slični diuretici uporabljivi su u liječenju blagih oblika HF-a, ali za teže oblike potrebni su jači diuretici. Furosemid, zaštićenim imenom Lasix („*lasts six hours*", traje šest sati), pojavio se kao spas. Uvođenje diuretika Henleove petlje furosemida i etakrinske kiseline ranih 60-ih godina prošloga stoljeća stubokom je unaprijedilo kliničku praksu. Dotad se HF smatrao terminalnim stanjem, ali su novi diuretici omogućili čudesno olakšanje od nakupljanja tekućine. Učinkovitost je bila očita pa su uvedeni u praksu i bez kliničkih ispitivanja. Furosemid kao arhetip potentnih diuretika Henleove petlje slijedili su već zaboravljeni etakrinska kiselina i bumetanid, sve do suvremenog takmaca torasemida. Furosemid je ostao temelj liječenja kongestivnog HF-a[12–14].

Spironolakton, neselektivni antagonist receptora aldosterona, pojavio se 1975. godine[15]. Samostalan mu je diuretski učinak slab, ali je sinergija s diureticima Henlove petlje jaka, a usto čuva kalij. Vrijednost spironolaktona iskazala se u

a framework for the basic concept of heart failure (HF). Ancient Greek and Roman physicians attributed edema, anasarca, and dyspnea to a variety of causes other than heart disease; pleural effusions were thought to originate in the brain, and the heart was believed to heat and distribute the vital spirit. Linking cardiac pathology to hemodynamic and clinical disorders following Harvey's discovery took time. G.M. Lancisi (1654-1720) observed that dilatation weakens the heart. J.N. Corvisart wrote in 1806 that marked cardiac dilatation in association with valvular regurgitation portends HF and a bad prognosis. In 1892, W. Osler viewed cardiac hypertrophy as a step towards HF ("broken compensation"). Those and many other physicians, whether famous or less known, elaborated the clinical presentation and course of HF[1–3].

Early pathophysiological concepts were simplistic, limited to cardiac weakness causing low cardiac output and extracellular fluid retention with pulmonary and systemic congestion. Treatment options were empirical and ineffective. Lifestyle changes provided some relief. Bloodletting and leeches were used for centuries. Southey tubes for edema drainage have been long forgotten. Among many herbal treatments that have been tried, only digitalis (foxglove) preparations proved to be a lucky hit. Since introduction to medical use by W. Withering in 1785, digitalis had been a pillar of HF treatment for about 200 years until recently[4–9].

Approaching modern times: the story of diuretics

The creation of effective diuretics in late the 1950s heralded the modern era of pharmacological HF management. Until 1957, the only diuretics used in HF were intravenous or intramuscular mercurial agents, which were difficult to use and fraught with toxicity. The serendipitous discovery of modern diuretics took place during the study of sulphonamide side-effects. In 1937/8, research on sulphonamides revealed their diuretic effects. In 1945, the development of the carbonic anhydrase inhibitor acetazolamide improved the understanding of diuretic mechanisms in renal tubules. Among many compounds synthesized in the search for potent carbonic anhydrase inhibitors, researchers stumbled on chlorothiazide, which inhibited not only carbonic anhydrase but also the sodium chloride cotransport system. Introduced in 1958, chlorothiazide was the first useful oral diuretic. It is still used widely, but much more as an antihypertensive agent than a HF drug[10–12].

Thiazides and thiazide-like diuretics may be useful in the management of mild HF, but more potent diuretics are needed in severe forms. Furosemide, with a brand-name Lasix ("lasts six hours"), came to the rescue. The introduction of the loop diuretics furosemide and ethacrynic acid in the early 1960s dramatically improved medical practice. Until then, HF had been considered a terminal condition, but new diuretics allowed amazing relief of fluid retention. It was obvious that they worked, and little in the way of clinical trials was needed to accept them in clinical practice. Furosemide, as an archetype of potent loop diuretics, was followed by now forgotten ethacrynic acid and bumetanide, in addition to its current rival torasemide, and has remained a cornerstone in the treatment of congestive HF[12–14].

Spironolactone, a nonselective steroid aldosterone receptor antagonist, appeared in 1957[15]. Its independent diuretic action is weak, but the synergism with loop diuretics is strong, in addition to potassium-sparing effects. The value of spironolactone became evident in the RALES trial (1999) which showed a reduction

istraživanju *RALES* (1999.) koje je pokazalo smanjenje pobola i smrtnosti u bolesnika s teškim HF-om[16]. Ti su podatci pospješili bitan zaokret u shvaćanju HF-a, upućujući na neurohormonalne učinke aldosterona. Selektivni antagonist receptora aldosterona epleronon učinkovit je kao aldosteron, ali bez neželjenih učinaka na receptore spolnih hormona[17]. Nakraju, novi nesteroidni antagonist receptora aldosterona finerenon u prednosti je u bubrežnih bolesnika s dijabetesom tipa 2[18].

Diuretici su prihvaćeni kao lijekovi koji očito olakšavaju tegobe i spašavaju život dok još nije bilo velikih kliničkih pokusa s krajnjim ishodima smrtnosti i preživljavanja. Čak i danas jedva da je moguće osmisliti takvu provjeru bez alternative potentnim diureticima[19,20].

Praksa, teorija i patofiziološke koncepcije

Digoksin, furosemid i spironlakton postavili su scenu za čin dinamičnog razvoja liječenja HF-a. Nekadašnja stagnacija i nemoć ustupili su mjesto aktivnomu traganju za napretkom u liječenju HF-a koje je obilježilo nadolazeća desetljeća. Ta je potraga oživjela istraživanja patofiziologije HF-a[21]. Istraživanja pretpostavljaju koncepcije koje čine temeljne modele HF-a. One su se uvelike izmijenile od sredine 20. stoljeća. Stariji ih se mogu prisjetiti iz vlastita profesionalnog iskustva. Izlaganja tih modela mogu se ponešto razlikovati, ali su neki modeli, npr. neurohormonalni model, širokoprihvaćeni. Milton Packer je predložio četiri koncepcije: 1) kardiorenalni model (40-e do 60-ih godina 20. st.), 2) kardiocirkulatorni model ili hemodinamska hipoteza (70-e i 80-e godine), 3) neurohormonalni model (od 90-ih sve donedavno) i 4) najnoviji model staničnoga stresa[22–24]. Takav se koncepcijski okvir čini zanimljivim jer može objasniti mnoge napretke, ali i neke stranputice. Pokušat ćemo izložiti ta shvaćanja uz kritičke napomene.

KARDIORENALNI MODEL

Kardiorenalni model prikazivao je HF kao edematozno stanje sa zadržavanjem soli i vode. Liječenje se temeljilo na digitalisu i diureticima. Premda je kongestija, tumačena uglavnom povećanim venskim tlakovima („zastoj"), dominirala konceptom, ni značenje premaloga minutnoga volumena („hipoperfuzija") nije se podcjenjivalo. Štoviše, renalna hipoperfuzija zbog maloga minutnog volumena smatrala se bitnom za zadržavanje izvanstanične tekućine zbog aktivacije renalnih (glomerularnih, tubularnih i peritubularnih) mehanizama. Oni su se mogli shvatiti kao atavistički odgovor na hipovolemiju zbog gubitka tekućine. Tijekom vremena koncept je proširen na adrenalne i neurohormonalne (npr. sekrecija antidiuretskog hormona) mehanizme zadržavanja volumena s dilucijskom hiponatremijom kao epifenomenom. Kasni su dodatci sinteza s neurohormonalnim konceptom HF-a. Nekadašnji kardiorenalni koncept vidi HF kao bolest srca s predvidivim renalnim odgovorom (bez bubrežne bolesti), za razliku od suvremenoga koncepta kardiorenalnog sindroma, u kojemu bolest bilo kojega od tih dvaju organa potiče bolest drugog[21,22].

Središnja postavka nekadašnjega kardiorenalnog sindroma podrazumijeva glavnu ulogu bolesti srca u patogenezi HF-a, dok se uloga bubrega smatrala sporednom. Raširenom uporabom preparata digitalisa (uglavnom digoksina) nastojala se popraviti slabost srca kao izvor HF-a. Procjena učinkovitosti i kliničke vrijednosti temeljila se na kliničkim opažanjima, iskustvu i prosudbi; tek poslije je provedeno nekoliko značaj-

in morbidity and death among patients with severe HF[16]. Those data suggested a paradigm-shift in the concept of HF, demonstrating the neurohormonal actions of spironolactone. The selective aldosterone receptor antagonist epleronone shares beneficial effects with spironolactone but is devoid of side-effects on sexual steroid hormones[17]. Finally, the use of a novel nonsteroidal aldosterone receptor antagonist fineronone is advantageous in patients with chronic kidney disease and type 2 diabetes[18].

Diuretics were accepted as symptom-relieving and lifesaving drugs before the days of large clinical trials with mortality and survival endpoints. Even nowadays, the lack of alternative to loop diuretics makes it hard to envision how to design such trials[19,20].

Practice, theories, and pathophysiological concepts

With digoxin, furosemide, and spironolactone available, the stage was set for a dynamic era of HF management. Past stagnation and incapacity gave way to active pursuit of advances in HF treatment that dominated in the decades to follow. This pursuit rekindled research on HF pathophysiology[21]. Research requires concepts that representing the basic models of HF. Those have changed significantly since the middle of the 20th century. Senior cardiologists may recall them from their own professional experience. The formulation of those models may vary somewhat, but some of them, e.g. the neurohormonal model, have been widely accepted. Milton Packer has proposed four concepts: 1) the cardiorenal model (1940s through the 1960s), 2) the cardiocirculatory model or hemodynamic hypothesis (1970s and 1980s), 3) the neurohormonal model (from 1990s up to recently), and 4) the recent cellular stress model[22–24]. Such a conceptual framework is interesting as it may explain many advancements but also some side-tracks. We will try to explicate the concepts, adding some remarks.

THE CARDIORENAL MODEL

The cardiorenal model regarded HF as an edematous disorder with salt and water retention. The pillars of treatment were digitalis and diuretics. Although the congestion seen to be due mostly to increased venous pressures ("backward HF") dominated the concept, low cardiac output ("forward HF") was duly appreciated. Moreover, renal hypoperfusion due to low cardiac output was deemed essential for extracellular fluid retention by activating renal (glomerular, tubular, and peritubular) mechanisms of volume conservation. These may be viewed as atavistic responses to hypovolemia due to fluid loss. In due course, the concept was expanded by adrenal and neurohormonal (e.g. antidiuretic hormone secretion) mechanisms of volume retention with dilutional hyponatremia as an epiphenomenon. Late additions were synthesis with the neurohormonal HF concept. The erstwhile cardiorenal concept views HF as a cardiac disorder with anticipatable renal response (without disease), at variance with the modern concept of cardiorenal syndrome where the disease of any of those two organs induces the disorder of the other[21,22].

The central tenet of the erstwhile cardiorenal concept assumes the main role of the heart disorder in the pathogenesis of HF, with the kidneys playing supporting roles. The widespread use of digitalis preparations (mostly digoxin) was intended to alleviate cardiac disorder as the origin of HF. The evaluation of efficacy and clinical utility was based on clinical

nih randomiziranih istraživanja s neutralnim rezultatima s obzirom na smrtnost[25–29]. Slab pozitivan inotropni učinak digitalisa inhibicijom Na^+/K^+ pumpe u srčanim miocitima s posljedičnim porastom koncentacije citosolnog Ca^{2+} preko Na^+/Ca^{2+} izmjene bio je precijenjen. Negativan kronotropni učinak, poželjan u tahikardiji zbog fibrilacije atrija bio je ograničen uskom terapijskom širinom. Usprkos ograničenjima, preparati digitalisa ostali su temelj liječenja HF-a tijekom dvaju stoljeća[6]. Možda i nije bila pogreška što je M. Packer na kongresu Europskoga kardiološkog društva (ESC) 2023. u svom *ESC Rene Laennec* predavanju iz kliničke kardiologije datirao kardiorenalni model u razdoblje 1748. – 1965. godine; uporaba digitalisa seže toliko unatrag[24].

Ipak, potentni diuretici nisu bili dostupni sve do 60-ih godina 20. st., kada je to razdoblje već bilo pri kraju. Diuretici su preokrenuli liječenje HF-a i ostali temelj njegova liječenja bez obzira na terapijsku koncepciju. Potrebni su kad god se pojavi višak izvanstanične tekućine[12,14].

Naposljetku, slijepo pridržavanje pretpostavki kardiorenalnog modela priječilo je napredak u liječenju HF-a. Snizivanje arterijskoga tlaka smatralo se opasnim zbog hipoperfuzije bubrega i miokarda. Vazodilatatori su se izbjegavali, osim u teškoj hipertenziji. Slično tomu, primjena beta-blokatora (BB) bila je sputana (propranolol se pojavio u 60-im godinama prošloga stoljeća kao antianginozni lijek) ne samo u strahom od hipotenzije nego i od negativne inotropije[22,30,31].

KARDIOCIRKULACIJSKI MODEL

Kardiocirkulacijski model ili hemodinamska hipoteza (1965. – 1992.), kako ga je obrazložio M. Packer, slijedio je kardiorenalni model. Potraga za novim strategijama liječenja, potaknuta iznevjerenim očekivanjima od digoksina i diuretika, vodila je preispitivanju patofizioloških poimanja. Novonastali obrat koncepcije sastojao se u shvaćanju da je HF načelno hemodinamski poremećaj koji uključuje cijeli srčanožilni sustav, ne samo srce nego i žile. Pažnja se umjesto na bubrege usredotočila na periferne žile i redistribuciju intravaskularnog volumena[22].

U HF-u adrenergička arterijska i venska vazokonstrikcija pogubno narušavaju hemodinamiku. Posljedični porast tlačnog opterećenja opire se protoku krvi i iscrpljuje miokard. Smanjenje venskog rezervoara povećava volumno opterećenje srca i pogoršava kongestiju. Opravdanje za primjenu **vazodilatatora** bilo je rasterećenje slabog srca od volumnog i tlačnog opterećenja, očekujući oporavak srčane funkcije[21,22]. Niz je vazodilatatora iskušan intravenski, ili peroralno, kako bi se suzbila vazokonstrikcija i ostvario napredak u liječenju. Stariji se kardiolozi mogu prisjeti straha da se ne izazove hipotenzija tim neuobičajenim terapijskim postupcima[31,32]. Primjena nekih vazodilatatora od kojih se u početku mnogo očekivalo, npr. od antagonista adrenergičkih alfa-receptora fentolamina i prazosina, završila je u slijepoj ulici[32–36]. Hidralazin i izosorbid dinitrat nisu ispunili očekivanja[36–38]. Mnogo se očekivalo i od blokatora kalcijskih kanala, ali su randomizirana klinička istraživanja pokazala da pogoršavaju HF[39–43]. Peroralni vazodilatatori u najboljem su slučaju pružali privremeno olakšanje, ali bez trajne koristi za ishode liječenja. Intravenska primjena vazodilatatora u akutnom HF-u pokazala se boljom opcijom, osobito uz hemodinamsko praćenje. Intravenski nitroglicerin, koji uglavnom djeluje kao venski dilatator, dragocjen je u akutnome kardiogenom plućnom edemu, dok se kombinirani arterijsko-venski dilatator natrijev nitroprusid

observations, experience, and judgement; only later were some respectable randomized trials conducted, with neutral results on mortality[25–29]. The weak positive inotropy of digitalis, due to the inhibition of Na^+/K^+-ATPase in cardiac myocytes with a consequent increase in cytosolic Ca^{2+} content through Na^+/Ca^{2+} exchanger, was overrated. Negative chronotropy, desirable in tachycardia due to atrial fibrillation, was limited because of narrow therapeutic width. Despite limitations, digitalis preparations had remained the mainstay of HF treatment for two centuries[6]. Perhaps M. Packer, when giving the European Society of Cardiology (ESC) Rene Laennec Lecture on Clinical Cardiology at the ESC Congress 2023, dated the cardiorenal model to the 1748-1965 period correctly; digitalis use dates back that far[24].

Potent diuretics became available not earlier than in the 1960s, when this period was at an end. The diuretics revolutionized HF treatment and have remained its mainstay irrespectively of the overall concept. They are needed whenever an excess of extracellular fluid arises[12,14].

Finally, sticking to the cardiorenal model impeded advances in HF treatment. Lowering arterial pressure was deemed risky because of renal and myocardial hypoperfusion. The use of vasodilators was avoided except in severe hypertension. Similarly, the use of beta-blockers (BB) was restrained (propranolol appeared in the 1960s as an antianginal drug), fearing not only arterial hypotension but also negative inotropy[22,30,31].

THE CARDIOCIRCULATORY MODEL

The cardiocirculatory model or the hemodynamic hypothesis (1965-1992), as it was formulated by M. Packer, followed the cardiorenal model. The quest for new treatment strategies spurred by the unmet expectations of digoxin and diuretics led to reappraisal of pathophysiological concepts. The ensuing paradigm shift viewed HF principally as a hemodynamic disorder involving the whole cardiovascular system, not only the heart but also the vessels. The focus shifted from the kidneys to peripheral vessels and redistribution of intravascular volumes[22].

In HF, adrenergically mediated arterial and venous vasoconstriction devastatingly impairs hemodynamics. The resulting increase in afterload exhausts the myocardium and impedes cardiac output. Reduction of the venous reservoir increases cardiac preload and aggravates congestion. The rationale for the use of **vasodilating drugs** was to relieve the failing heart of preload and afterload burden, expecting a recovery in cardiac function[21,22]. The whole array of vasodilators was tested intravenously or orally to relieve vasoconstriction and to achieve a breakthrough in HF management. Senior cardiologists may recall the fear of causing hypotension with those unorthodox innovations[30,31]. The use of some initially promising vasodilators, e.g. the adrenergic alpha-receptor blockers phentolamine and prazosin, remained a dead-end attempt[32–36]. Hydralazine and isosorbide dinitrate held some promise, which was not fulfilled[36–38]. Calcium channel blockers were expected to improve hemodynamics, but controlled clinical trials showed worsening of HF[39–43]. At best, oral vasodilators provided some temporary relief without long-term benefits on outcomes. Intravenously administered vasoactive agents for acute HF fared better, especially if guided by hemodynamic monitoring. Intravenous nitroglycerine, acting mostly as a venous vasodilator, is still valuable in acute cardiogenic pulmonary edema, while combined arterial and venous vasodilator sodium nitroprusside is helpful in severe acute HF in a critical care setting[44–47].

primjenjuje u teško akutnom HF-u u jedinicama intenzivne skrbi[44–47].

Razočaranje oralnim vazodilatatorima skrenulo je pozornost na samo srce. Kako se poremećaj kontraktilnosti miokarda smatrao osnovnim problemom, stvoren je niz lijekova s pozitivnim **inotropnim** učinkom. Pristup se temeljio na jačanju kontraktilnosti poticanjem utoka kalcijskih iona ili održavanjem veće koncentracije tih iona u citosolu srčanih miocita tijekom trajanja akcijskog potencijala. Desetci su takvih lijekova napredovali do 3. faze kliničkih istraživanja. Među njima su najviše obećavali dobutamin, amrinon, milrinon, enoximon, levosimendan, pimobendan i ksamoterol. Prvi je od njih bio dopamin, stvoren 1975. modifikacijom molekule izoproterenola. Svrha je bila iskoristiti adrenergičku stimulaciju miokarda, ali izbjeći pogubnu vazokonstrikciju. Slijedio je niz inhibitora fosfodiesteraze 3 (PDE-3), prvo amrinon, potom milrinon i enoximon. U 80-ima prošloga stoljeća razvijani su kalcijski senzibilizatori s levosimendanom kao prototipom. On pojačava senzitivnost kontraktilnog aparata na kalcijske ione tijekom sistole, ali ne priječi njihovo otpuštanje u dijastoli. Levosimendan, usto, inhibira PDE-3 i aktivira K^+ osjetljive kanale uzrokujući jaku vazodilataciju. Pimobendan ujedinjuje učinke kalcijskih senzibilizatora i PDE-3 inhibitora. Ksamoterol je $beta_1$ selektivni parcijalni adrenergički agonist. Ideal je bio razviti lijek s pozitivnim inotropnim, a, usto, i vazodilatacijskim učinkom kao levosimendan, ili vazodilatator s pozitivnim inotropnim učinkom kao flosekvinan. Taj lijek ima oba svojstva, vazodilatacijsko i pozitivno inotropno, koja nisu sasvim razjašnjena, ali se čini da su različita od agonista adrenergičkih receptora i PDE inhibitora[48].

Navedeni, a i drugi lijekovi s pozitivnim inotropnim učinkom, neovisno o načinu djelovanja, postizali su privremeno hemodinamsko i kliničko poboljšanje, ali nisu smanjivali smrtnost i pobol. Štoviše, povezivali su se s povećanom smrtnošću, osim prognostički neutralnog digoksina[25,48,49]. Stvoreni su mnogi inotropni lijekovi, ali su u uporabi ostali samo oni pripravljeni za kratkotrajnu intravensku primjenu (npr. 48 sati) u akutnom HF-u. Dobutamin, milrinon i levosimendan još su nezamjenjivi u našim jedinicama intenzivne skrbi[50–53].

Nedostatak inotropnih lijekova da pretvore kratkotrajna poboljšanja u dugotrajnu korist može se objasniti samo pretpostavkama. Pojednostavnjeno je objašnjenje da preopterećenje skraćuje vijek ozlijeđenog organa. Pretjerana stimulacija rasipa ionako oskudne zalihe energije. Trajna je adrenergička stimulacija pogubna, a BB smanjuju smrtnost i pobol. Usto, kronična uporaba lijekova koji djeluju preko cAMP modulacije, kao što su PDE-3 inhibitori i adrenergički stimulansi, remeti homeostazu iona kalcija s desenzitizacijom kontraktilnog aparata, poremećajem relaksacije u ranoj dijastoli i ventrikularnim aritmijama. Poremećaji energijske ravnoteže i homeostaze kalcijskih iona pogubni su za srčane miocite. Nadalje, HF je heterogen sindrom koji uključuje širok raspon raznih bolesti. Opasnosti od kroničnog liječenja milrinonom bile su uočljivo češće u ishemijskom nego u neishemijskom obliku HF-a. Doze inotropnih lijekova možda su bile prevelike, odmjerene tako da postignu najveći neposredan inotropni učinak bez obzira na kasne posljedice. U dvama stoljećima povijesti digitalisa mnogo je analogije s uporabom inotropa u 80-im godinama 20. st. u pogledu pretjerane uporabe i predoziranja. Razboritija uporaba i probir bolesnika mogli su uroditi drukčijim ishodima[48,49,54].

Disappointment with oral vasodilators shifted the focus to the heart itself. As the impairment of myocardial contractility was deemed to be the primary problem, the whole array of **inotropic agents** was created. The basic approach was to increase contractility, stimulating the influx of calcium ions or maintaining higher calcium levels in the cytosol of cardiac myocytes throughout the action potential. Dozens of such drugs progressed to phase 3 clinical trials. Among them, dobutamine, amrinone, milrinone, enoximone, levosimendan, pimobendane, and xamoterol were the most promising. Dobutamine was the first of them, created in 1975 by modifying the chemical structure of isoproterenol. The rationale was to benefit from adrenergic stimulation but to avoid detrimental vasoconstriction. A series of phosphodiesterase 3 (PDE-3) inhibitors followed, amrinone first, followed by milrinone and enoximone. Calcium sensitizers were developed in the 1980s, with levosimendan as a prototype. It increases contractile apparatus sensitivity to calcium ions during systole, not interfering with their diastolic release. Levosimendan also inhibits PDE-3 and activates ATP sensitive K^+ channels, causing strong vasodilation. Pimobendan shares calcium sensitizing and PDE-3 inhibiting effects. Xamoterol is a beta1 selective partial adrenergic agonist. The ideal was to develop a positive inotropic agent with vasodilator properties, like levosimendan, or a vasodilator with positive inotropic properties, like flosequinan. This drug has both vasodilating and inotropic properties that are not entirely understood but are believed to be distinct from β-adrenergic receptor agonists and PDE inhibitors[48].

Those and other positive inotropic agents, irrespective of mode of action, provided a transient hemodynamic and clinical improvement but failed to reduce mortality and morbidity. Moreover, they were associated with increased mortality, except the prognostically neutral digoxin[25,48,49]. Many inotropic drugs were created, but only those designed for short-term intravenous use (e.g. 48 h) in severe acute HF remained in use. Dobutamine, milrinone, and levosimendan are still indispensable in our cardiac care units[50–53].

The failure of inotropic agents to convert short-term improvements into long-term benefits, with an excess of mortality, can be explained only speculatively. A mechanistic explanation suggests that overstrain of an injured organ shortens its lifespan. Overstimulating sick myocardium unduly depletes its meagre stores of energy. The persistent adrenergic overstimulation is detrimental, whereas BBs reduce mortality and morbidity. In addition, the chronic use of drugs acting via cAMP modulation, like PDE-3 inhibitors and adrenergic stimulants, disrupts calcium homeostasis with desensitization of the contractile apparatus to calcium through impairment of early diastolic relaxation and ventricular arrhythmias. Disruption of cardiac myocyte energetics and calcium ion homeostasis are detrimental for cardiac myocytes. Furthermore, HF is a heterogeneous syndrome comprising a diverse spectrum of diseases. The harmful effects of chronic treatment with milrinone were conspicuously more prevalent in ischemic than in non-ischemic HF. The doses of inotropic agents used were perhaps too high, adjusted to achieve maximal immediate inotropic effect, notwithstanding later consequences. The two-century-long history of digitalis parallels the positive inotropes of the 1980s in overuse and overdosage deviations. More judicious and selective use of those inotropes may have yielded different end-results[48,49,54].

Čak ako su pokušaji da se HF liječi inotropima propali, sama koncepcija ne mora biti osuđena na neuspjeh. Jačanje slaboga srca bio prvi i sam po sebi razumljiv cilj naraštajima liječnika, utjelovljen u iluziji o moćnoj inotropiji digitalisa. Još se očekuje da će pozitivni inotropi imati važnu ulogu u liječenju kroničnog HF-a, ali u okviru pomno razrađene koncepcije, a ne nasilnim pokretanjem već iscrpljenog miokarda. Zastoj u razvoju pozitivnih inotropa slijedili su novi stanični ciljevi u 2000-im godinama. Farmakološki i genski terapijski pristupi bili su usmjereni na ključan enzim koji regulira homeostazu kalcija u miokardu, a potisnut je u HF-u: Ca^{2+} ATPazu sarkoplazmatskog retikula (SERCA 2A). Drugi se pristup odnosio na miozinske aktivatore, novu skupinu tzv. miotropa, lijekova koji poboljšavaju funkciju miokarda izravnim učinkom na sarkomeru. Omekamtiv mekarbil, prvi u toj skupini, jača kontraktilnost miokarda selektivnim vezivanjem za srčani miozin, povećavajući broj miozinskih glava koje se mogu vezati za aktinske filamente i pojačati kontrakciju na početku sistole[48,54]. Istraživanje *GALACTIC-HF-a* pokazalo je da omekamtiv mekarbil smanjuje skupnu incidenciju HF-a i kardiovaskularne (CV) smrti u bolesnika s HF-om i reduciranom ejekcijskom frakcijom (HFrEF)[55,56]. Agencija za hranu i lijekove Sjedinjenih Američkih Država (FDA) odbila je odobriti omekamtiv mekarbil uz obrazloženje nedostatka dokaza o djelotvornosti (2023.). Nijedan pozitivan inotrop nije zasada odobren za dugotrajnu uporabu u HF-u.

M. Packer, koji je opisao hemodinamski model HF-a, u svojemu izvornom članku (1993.) nije posvetio veću pažnju spoznaji da dijastolička disfunkcija lijeve klijetke (LV) može biti uzrok HF-a. Premda su odnosi tlaka i volumena tijekom srčanog ciklusa otkriveni još početkom 20. stoljeća, a pojam luzitropije LV-a koji označuje brzinu (rano)dijastoličke relaksacije prethodio je kliničkim spoznajama, klinička istraživanja nisu prepoznala značenje dijastoličke disfunkcije LV-a do 1970-ih, a klinička praksa do 1980-ih[57–66]. To je bila prava prekretnica jer se dotada smo poremećaj sistoličke funkcije LV-a (hipokontraktilnost) smatrao uzrokom HF-a. Tek tada je uočeno da je u ~40 – 50 % bolesnika s HF-om sistolička funkcija LV-a očuvana. Vjerovalo se da je dijastolička disfunkcija glavni uzrok HF-a u najmanje 30 % svih slučajeva HF-a[62,67–69].

Iskrsnulo je zbunjujuće pitanje kako liječiti takve bolesnike. Pozitivni su se inotropi činili besmislenima, a diuretici nužnima; višak je tekućine u svakom slučaju trebalo ukloniti. Uočeno je da je to potrebno učiniti oprezno jer je Frank Starlingova krivulja strma i pomaknuta udesno. Stoga bi nagao gubitak intravaskularnog volumena mogao uzrokovati iznenadan pad udarnog i minutnog volumena. Mnoga mala, a potom i neka prijelomna klinička istraživanja o liječenju hipertenzije pokazala su da su inhibitori renin-angiotenzin-aldosteronskog (RAAS) sustava bolji nego BB za oporavak dijastoličke funkcije LV-a usporedo s regresijom hipertrofije. Produljenje dijastole uz BB ipak je korisno za dijastoličku funkciju. Blokatori kalcijskih kanala pokazali su se prijepornima. Podatci o učinkovitosti takvih terapijskih postupaka u HF-u su se na indicije temeljene na hemodinamskim nadomjestcima ishoda, bez podataka o pobolu i smrtnosti[66,70,71].

Nedoumice o liječenju HF-a uzrokovana dijastoličkom disfunkcijom LV-a nikad nisu bile razriješene kliničkim istraživanjima jer je hemodinamska hipoteza izgubila na važnosti. Procjena dijastoličke funkcije LV u kliničkoj praksi je često dvojbena[72,73]. Razvoj koncepcije razjasnio je da se HF s oču-

Even if the attempts to treat HF with inotropes failed, the concept itself may not be doomed to failure. Strengthening the weak heart was the primordial aim which appeared self-evident for generations of physicians and was incorporated in wishful thinking on digitalis inotropy. Positive inotropes are still expected to have significant roles in chronic HF treatment, but as part of an elaborate framework of concepts and not as a blunt overstimulation of already exhausted cardiac myocytes. A hiatus in the development of positive inotropes was followed by new cellular targets in the 2000s. Pharmacological and gene therapy approaches were directed at a key enzyme responsible for myocardial calcium homeostasis that is downregulated in HF: sarcoplasmic reticulum Ca^{2+}-ATPase (SERCA2a). Another concept is related to cardiac myosin activators, which are a new class of myotropes that improve myocardial function by directly augmenting cardiac sarcomere function. Omecamtiv mecarbil, the first of this class, augments cardiac contractility by selectively binding to cardiac myosin, thus increasing the number of myosin heads that can bind to the actin filament and initiate a power stroke at the start of systole[48,54]. The GALACTIC-HF trial (2021) showed that omecamtiv mecarbil reduced the incidence of a composite of a heart failure events and death from cardiovascular causes among patients with HF with reduced ejection fraction (HFrEF)[55,56]. However, FDA has declined to approve omecamtiv mecarbil, citing a lack of evidence on efficacy in 2023. No positive inotrope is currently approved for long-term use in HF.

M. Packer, who formulated the hemodynamic model of HF in his original article (1993), did not pay much attention to the recognition of diastolic left ventricular dysfunction as the cause of HF. Though the pressure-volume relations during the cardiac cycle had already been recognized in the early 20th century and the term left ventricular lusitropy, denoting the rate of early diastolic relaxation, predated clinical concepts, clinical research did not recognize the concept of left ventricular diastolic dysfunction until the 1970s and clinical practice did not use it until the 1980s[57–66]. This was a real paradigm shift, since until then only the impairment of left ventricular systolic function (i.e. contractility) was regarded as a cause of HF. It was only then that cardiologists realized that left ventricular systolic function was preserved in 40-50% of HF cases. It was assumed that diastolic dysfunction was the main culprit, accounting for at least 30% of all HF cases[62,67–69].

This led to the confusing question of how to treat those patients. Use of positive inotropic agents seemed senseless and diuretics necessary; the excess of fluid should be removed in any case. It was advised to do this cautiously, since the Frank Starling curve was supposed to be steep and shifted to the right. Therefore, a sudden contraction of intravascular volume could precipitate a sudden drop in stroke volume and cardiac output. Many small clinical studies and later some landmark hypertension trials showed that renin-angiotensin-aldosterone system (RAAS) antagonists may improve left ventricular diastolic function in parallel with left ventricular hypertrophy regression better than BBs. The latter may yet provide beneficial effects on diastolic function by prolonging diastole. Calcium channel blockers proved to be controversial. The evidence on efficacy of those treatments in HF was only circumstantial, limited to surrogate hemodynamic data without the data on morbidity and mortality outcomes[66,70,71].

The uncertainties about the treatment of HF due to the left ventricular diastolic dysfunction have been never resolved by clinical trials since the hemodynamic hypothesis fell into disrepute. The assessment of left ventricular diastolic dysfunc-

vanom sistoličkom funkcijom ne može jednostavno svesti na dijastoličku disfunkciju. Uloga dijastoličke disfunkcije za patofiziologiju HF-a nije zanemarena, nego je uključena u cjelovite koncepcije HF-a s očuvanom sistoličkom funkcijom, normalnom ejekcijskom frakcijom (HFnEF) i očuvanom ejekcijskom frakcijom (HFpEF)[74–79]. Te su koncepcije nadrasle hemodinamski okvir[77–81].

NEUROHORMONALNA HIPOTEZA

Neurohormonalna hipoteza (1992. – 2019.), kako ju je nazvao, opisao i datirao M. Packer, značila je radikalan preokret u poimanju i proboj koncepcije sa sagledavanjem HF-a kao sistemske bolesti sa složenim neurohormonalnim odgovorom uz RAAS i adrenergički sustav u glavnim ulogama[21–23]. Stariji se mogu prisjetiti da se taj pristup pojavio neprimjetno, ne kao plod inventivnog razmišljanja koje bi revidiralo patofiziološke predodžbe, već empirijski kroz istraživanja s vazodilatatorima. Prvi ACE inhibitor kaptopril, prvotno izoliran iz zmijskog otrova, uveden 1981. i u početku shvaćen kao obični vazodilatator koristan za liječenje arterijske hipertenzije, pokazao se boljim od prazosina, hidralazina i drugih „čistih" vazodilatatora u liječenju kroničnog HF-a. Prednost je protumačena zaprječavanjem pogubnih neuroendokrinih odgovora[34–36,82]. Nakon kaptoprila, razvijeni su mnogi drugi ACE inhibitori sa specifičnim odlikama. Oni su postigli kvantni skok u liječenju bolesti širom CV kontinuuma. Niz prijelomnih kliničkih istraživanja liječenja kroničnog HF-a s oštećenom sistoličkom funkcijom pokazao je da ACE inhibitori ne postižu samo prolazna hemodinamska poboljšanja nego i dugotrajno smanjenje morbiditeta i mortaliteta. Prijelomna istraživanja najveće važnosti bila su sljedeća: *CONSENSUS I* (enalapril, 1987.), *VHeFT I* (enalapril, 1991.), *SOLVD* (enalapril, 1991.), *SAVE* (kaptopril nakon infarkta miokarda, 1992.), *AIRE* (ramipril nakon infarkta miokarda, 1993.) i TRACE (trandolapril, nakon infarkta miokarda, 1995.)[83–89].

Dotad neviđeni proboj u spoznajama o HF-u kroz klinička istraživanja s ACE inhibitorima osnažio je interes za eksperimentalna istraživanja RAAS-a, kako bi se objasnili rezultat i zacrtao daljnji napredak. Spoznalo se da je, osim endokrinog RAAS-a, bitan i široko rasprostranjen tkivni RAAS, sa srcem, žilama, živčanim sustavom i bubrezima u glavnim ulogama. Otkriveni su putevi molekularne signalizacije endokrinog (u krvi), parakrinog (u tkivima) i intrakrinog (u stanicama) RAAS-a, s autokrinom i jukstakrinom komponentom. RAAS je prepoznat kao sveprisutan sustav bitan za očuvanje homeostaze, ali i za razvoj bolesti, s temeljnim biološkim značenjem i dubokim evolucijskim korijenima, načinjen od prastarih molekula. Ključna molekula angiotenzin II, oktapeptid s jakim vazokonstrikcijskim učincima, pojavila se u ranom kambriju prije oko 500 milijuna godina, primarno kao epigenetski regulator sinteze proteina i faktor rasta. Ujedno je to i ključna molekula u putevima signalizacije patološke hipertrofije miokarda i promotor ateregeneze[90–94].

Do 90-ih godina prošloga stoljeća pozitivni inotropni lijekovi (uglavnom digoksin) smatrali su se temeljem liječenja HF-a. Kako se slaba sistolička funkcija LV-a smatrala glavnim uzrokom HF-a, svi lijekovi s negativnim inotropnim učinkom smatrali su se „apsolutno kontraindiciranima" prema smjernicama za kliničku praksu, sve do 1995. g[95]. Zamisao o uporabi BB-a kao osnovnog lijeka za liječenje HF-a kako bi se olakšale tegobe i produljio život, činila se proturječnom i nepriličnom. Kardiološka javnost sa skepsom i nevjericom

tion in clinical practice is often indeterminate or elusive[72,73]. The conceptual advancements made clear that HF in patients with preserved systolic function cannot be simplistically reduced to diastolic dysfunction. The role of left ventricular diastolic dysfunction in the pathophysiology of HF has not been ignored but has instead been incorporated into broader and more comprehensive concepts of HF with preserved systolic function, normal ejection fraction (HFNEF), and preserved ejection fraction (HFpEF)[74–79]. These concepts outgrew the hemodynamically frame[77–81].

THE NEUROHORMONAL HYPOTHESIS

The neurohormonal hypothesis (1992-2019), as it was named, formulated, and dated by M. Packer, presented a radical paradigm-shift and a conceptual breakthrough which viewed HF as a systemic disorder involving a complex neurohormonal response with renin-angiotensin-aldosterone (RAAS) and adrenergic systems in protagonist roles[21–23]. Senior cardiologists may remember that this approach emerged gradually, not because of ingenious thinking which revised pathophysiological concepts but rather arising empirically through studies on vasodilators. The first angiotensin converting enzyme inhibitor (ACEi) captopril, first isolated from snake venom, introduced in 1981 and initially considered a plain vasodilator useful in arterial hypertension, proved to be superior to prazosin, hydralazine, and other pure vasodilators in the treatment of chronic HF. The advantage was explained by the blockade of detrimental neuroendocrine responses[34–36,82]. Following captopril, many other ACEis with specific qualities were developed. They provided a quantum leap in the treatments across the cardiovascular continuum. A series of landmark clinical trials evaluating the treatment of chronic HF with impaired left ventricular systolic function demonstrated that ACEis provided not only short-term hemodynamic improvements but also long-term benefits to morbidity and mortality. The most cited game-changing trials were CONSENSUS I (enalapril, 1987), VHeFT I (enalapril, 1991), SOLVD (enalapril, 1991), SAVE (captopril after myocardial infarction, 1992), AIRE (ramipril after myocardial infarction, 1993), and TRACE (trandolapril, after myocardial infarction, 1995)[83–89].

An unprecedented breakthrough in HF trials with ACEs reinvigorated experimental scientific research on RAAS to explain those results and chart further advances. It became clear that besides of the endocrine component of RAAS, there was also a widespread tissue RAAS, with the heart, vessels, nervous system, and the kidneys as the main players. Endocrine (in blood), paracrine (in the tissues), and intracrine (in the cells), signaling was identified in addition to autocrine and juxtacrine RAAS. RAAS was recognized as a ubiquitous system for homeostasis and pathologies, biologically fundamental, with deep evolutionary roots and composed of ancient molecules. Its pivotal molecule, angiotensin II, an octapeptide with strong vasoconstrictive properties, arose in the early Cambrian ~500 million years ago, primarily as an epigenetic regulator of protein synthesis and growth-promoting factor. It is a key molecule in the signaling pathway of pathological myocardial hypertrophy and a potent promotor of atherogenesis[90–94].

Until the 90s, positive inotropic agents (mainly digoxin) were deemed a mainstay of HF treatment. As the poor left ventricular systolic function was viewed as the main cause of HF, all drugs with negative inotropic effect were "absolutely contraindicated" according to the practice guidelines up to 1995[95]. The idea of using BBs as a primary therapy for congestive HF to

odgovorila je na pionirski izvještaj Waagsteina *i sur.* u kojemu je prikazao 7 bolesnika s dilatacijskom kardiomiopatijom i refraktarnim HF-om uspješno liječenih danas već zaboravljenim alprenololom i praktololom[96,97]. Toliko heretički pristup mogao se shvatiti kao očajničko traženje izlaza u bezizlaznoj situaciji. Waagstein je prekršio tabu i pobudio proturječje. Mijena shvaćanja je potrajala. Mnoštvo malih istraživanja s nadomjesnim ishodima samo je pogoršalo zbrku. Bila su potrebna desetljeća da znanstvena istraživanja prepoznaju pogubne učinke neprikladnoga adrenergičnog odgovora na slabljenje sistoličke funkcije i opravdaju velika randomizirana klinička istraživanja[98]. Metodologija je već bila usavršena u kliničkim istraživanjima primjene ACE inhibitora u HF-u. Prijelomna klinička istraživanja uvjerljivo su dokazala učinkovitost četiriju BB-a u smanjenju pobola i smrtnosti u bolesnika sa „sistoličkim" HF-om. Vodeća su istraživanja bila: *CIBIS I* (bisoprolol, 1994.), *CIBIS II* (bisoprolol, 1999.), *US Carvedilol Heart Failure Trials Program* (karvedilol, 1996.) i *MERIT-HF* (metoprolol, 2000.)[99–103]. Uslijedila su i druga važna istraživanja s bisoprololom, karvedilolom i metoprololom, dok se istraživanje *SENIORS* koje je afirmiralo nebivolol pojavilo 2005. godine[104].

Dok su ACE inhibitori uvedeni u liječenje HF-a kao vazodilatatori da poboljšaju hemodinamiku, a tek poslije su prepoznati kao neurohormonalni lijekovi, BB su primarno uvedeni kao neurohormonalni lijekovi. Kad je M. Packer predložio svoj neurohormonalni model patofiziologije HF-a 1993. g., BB su bili zamišljeni, ali ne i provjereni u kliničkim istraživanjima, niti odobreni za liječenje HF-a[23]. Ta su istraživanja uvela BB u široku uporabu za liječenje „sistoličkog" HF-a i učvrstila neurohormonalni model. ACE inhibitori i BB preuzeli su vodstvo u smjernicama za liječenje HF-a na objema stranama Atlantika dijeleći dva vodeća mjesta[46,105].

Neurohormonalni je model potaknuo reevaluaciju spironolaktona. Nakon 40 godina u skromnoj ulozi dodatnog diuretika za štednju kalija, nakon istraživanja *RAALES* (1999.), spironolakton je promaknut kao bitan neurohormonalni lijek koji smanjuje pobol i smrtnost u bolesnika s HF-om[16]. Imajući u vidu ključnu ulogu aldosteronskih receptora u patogenezi srčanožilnih i bubrežnih bolesti, rezultati istraživanja *RAALES* možda su se mogli očekivati, ali je jasno smanjenje rizika od smrti zbog bilo kojeg uzroka poslalo jasnu poruku. Istraživanje *EPHESUS* (2003.) pokazalo je da selektivni blokator receptora aldosterona epleronon smanjuje smrtnost i pobol u bolesnika s HF-om zbog akutnog infarkta miokarda[17]. Ti su podatci učvrstili antagoniste mineralokortikoidnih receptora (MRA) na trećem mjestu popisa lijekova izbora za liječenje HF-a, nakon ACE inhibitora i BB-a, dok je digoksin spušten na nisku četvrtu poziciju[106,107].

Istraživanje angiotenzina II urodilo je 1992. pronalaskom losartana, antagonista receptora angiotenzina II tipa 1 s antihipertenzivnim svojstvima[108]. On je bio prethodnik čitave skupine blokatora angiotenzinskih receptora (ARB) koji se od tada uporabljuju kao zamjena ACE inhibitorima. Slijedili su kandesartan, eprosartan, irbesartan, valsartan, telmisartan i olmesartan. Potvrđen kao antihipertenzivni lijek koji čuva srce i bubrege (*RENAAL* 2001.; *LIFE* 2002.), losartan je uspoređivan s kaptoprilom u liječenju sistoličkog HF-a (*ELITE I* 1997.; *ELITE II* 2000.) i akutnog infarkta miokarda (*OPTIMAAL* 2002.), dokazujući neinferiornost uz bolju podnošljivost[70,109–113]. Klinička istraživanja s novijim lijekovima skupine ARB potkrijepila su poruku: ARB su ravnopravna alternativa ACE inhibitorima

improve symptoms and prognosis seemed paradoxical and dissenting. The cardiac community reacted with skepticism and disbelief when, in 1975, the pioneering report of Waagstein *et al.* gave an account on 7 cases of refractory HF in patients with dilated cardiomyopathy treated successfully by already forgotten BBs alprenolol and practolol[96,97]. This unorthodox approach may be viewed as a bailout in a desperate situation. Waagstein violated a taboo and stirred controversy. A change of opinion took time. Many small studies with surrogate endpoints only added to confusion. Decades were needed for scientific research to recognize the detrimental effects of maladaptive adrenergic response to declining systolic function and vindicate large controlled clinical trials[98]. The methodology was honed in HF trials with ACEs. Landmark clinical trials convincingly demonstrated the efficacy of four BBs in improving morbidity and reducing mortality in the patients with "systolic" HF. Pioneering trials were: CIBIS I (bisoprolol, 1994), CIBIS II (bisoprolol 1999), US Carvedilol HF Trials Program (1996, carvedilol), and MERIT-HF (metoprolol, 2000)[99–103]. Other important trials with bisoprolol, carvedilol, and metoprolol followed, while the SENIORS trial affirming nebivolol took place slightly later (2005)[104].

While the ACEIs were introduced as vasodilators in the treatment of HF to improve hemodynamics and were only later recognized as neurohormonal agents, BBs were introduced primarily as neurohormonal agents. When M. Packer proposed his neurohormonal model of HF pathophysiology in 1993, BBs were only envisaged, but neither evaluated in clinical trials nor approved for the treatment of HF[23]. The trials opened the door to the extensive use of BBs in the treatment of "systolic" HF and firmly established the neurohormonal concept. ACEIs and BBs took pole position in the guidelines for HF treatment on both sides of the Atlantic, sharing the first two positions[46,105].

The neurohormonal concept led to reappraisal of spironolactone. After 40 years spent in a modest role as an adjunct potassium sparing diuretic, following the RAALES trial (1999) spironolactone was revisited as an essential neurohormonal drug which reduces morbidity and mortality in patients with HF[16]. Considering the key role of aldosterone receptors in the pathogenesis of cardiovascular and renal pathologies, the results of RAALES trial might have been expected, but the clear reduction in all-cause mortality sent a clear message. The EPHESUS trial (2003) showed that the selective aldosterone receptor blocker eplerenone reduced mortality and morbidity in patients with acute myocardial infarction complicated by HF[17]. This evidence positioned mineralocorticoid receptor antagonists (MRAs) firmly in third place on the list of preferred HF drugs, after ACEIs and BBs, while digoxin was relegated to the low fourth position[106,107].

In 1992, research on angiotensin II led to losartan, an angiotensin II type 1 receptor antagonist with antihypertensive properties[108]. It was a forerunner of the whole class of angiotensin receptor blockers (ARBs) which have been used as an alternative to ACEs ever since. Candesartan, eprosartan, irbesartan, valsartan, telmisartan, and olmesartan followed. Affirmed as an antihypertensive drug with heart and kidney protecting properties (RENAAL 2001; LIFE 2002), losartan was compared to captopril in the treatment of systolic HF ((ELITE I 1997; ELITE II, 2000) and acute myocardial infarction (OPTIMAAL 2002), showing non-inferiority with better tolerability[70,109–113]. The trials with newer ARBs upheld the message: ARBs are a noninferior alternative to ACEs in left ventricular systolic failure. Only

u sistoličkom zatajivanju LV-a. Samo valsartan (2001.), kandesartan (*CHARM-Alternative* 2003.; *CHARM-Added* 2003.), ponovno losartan (*HEAAL* 2012.) te u manjem opsegu telmisartan (1999., 2010.) su vrednovani u istraživanjima sa „sistoličkim" HF, dok su kandesartan (*CHARM-Preserved*, 2003.) i irbesartan (2008.) procjenjivani u istraživanjima HF-a s očuvanom sistoličkom funkcijom[114–121]. Europske smjernice za HF (2021.) ne iskazuju prednost u izboru između ACE inhibitora i ARB skupine, nego ih preporučuju kao alternativu (IA). Američke smjernice (2022.) daju prednost ACE inhibitorima u bolesnika koji nisu primali nijedan lijek iz tih dviju skupina[46,105].

Uporaba lijekova iz skupine u ARB liječenju bolesnika s HFrEF-om nedavno je podignuta na viši stupanj dodatkom inhibicije neprilizina, što se dobro uklapa u neurohormonalnu koncepciju HF-a[122]. U istraživanju *PARADIGM-HF* (2014.) dvostruko djelujuća kombinacija inhibitora receptora angiotenzina II i inhibitora neprilzina (ARNI) sakubitril/valsartan smanjila je zajedničku učestalost hospitalizacije zbog HF-a i smrtnosti u usporedbi sa standardnim liječenjem enalaprilom[123,124]. Primjena ARNI danas je prihvaćena kao neprijeporna („class I") indikacija za liječenje bolesnika s HFrEF-om [46,105,125].

Tijekom evolucije uvelike očuvanu obitelj natriuretskih peptida čine atrijski, moždani i C-tip peptida (ANP, BNP i CNP). ANP i BNP luče atriji i ventrikuli, a djeluju preko receptora natriuretskih peptida tipa A (NPR-A) i tipa B (NPR-B) koji povezani s guanil ciklazom posreduju u postizanju bioloških učinaka. Oni uključuju vazodilataciju, natriurezu i diurezu te inhibiciju RAAS-a, endotelina i vazopresina, zajedno s mobilizacijom lipida. Endopeptidaza neprilizin brzo razgrađuje ANP. Inhibicija neprilizina podiže razinu ANP-a u krvotoku s povoljnim učincima na HF[122,126,127].

Sagledavanje HF-a kroz hipotetske mehanizme ne mora odražavati složenu kliničku stvarnost. Nadobudne se zamisli često ne obistine u kliničkoj praksi. Klinički pokusi mogu raspršiti očekivanja. Nesiritid, humani rekombinantni natriuretski peptid B-tipa (BNP) koji potiče vazodilataciju, veže se na receptore u krvnim žilama, bubrezima i u drugim organima oponašajući učinke endogenih natriuretskih peptida. FDA ga je odobrila 2001. za primjenu u bolesnika s akutnim HF-om na temelju istraživanja koja su pokazala umjerena hemodinamska i simptomatska poboljšanja. Nekoliko godina nakon odobrenja (2005.) nesiritid se prestao rabiti jer se činilo da mala istraživanja upozoravaju na rizik od oštećenja bubrega i povećanu smrtnost. Istraživanje *ASCEND-HF* (2011.) nije pokazalo učinak nesiritida na smrtnost i hospitalizaciju zbog HF-a[128–132].

Povećana frekvencija srca u mirovanju povezuje se s lošim ishodima u bolesnika s kroničnim sistoličkim HF-om. U liječenju bolesnika s HFrEF-om neurohormonalnim se lijekovima može dodati ivabradin kao dopuna da uspori sinusni ritam. On inhibira „čudnu" I_f struju vodiča u sinusnome čvoru, bez utjecaja na AV čvor, inotropiju, dijastoličku funkciju, minutni volumen, vaskularni otpor, ili arterijski tlak[133,134]. Ivabradin bi se trebao razmotriti (II. a indikacija) u liječenju bolesnika u sinusnom ritmu s LVEF ≤35 % i frekvencijom srca u mirovanju ≥70/min koji su simptomatski unatoč optimalno doziranoj terapiji koja uključuje BB, ACEi/ARNi i MRA (ili u onih koji ne podnose BB) da se smanje rizici od hospitalizacije zbog HF-a i CV smrti[46]. Ivabradin nije zamjena za BB[133].

Neurohormonalna aktivacija ključan je mehanizam u progresiji HF-a, a terapijski antagonizam neurohormonalnih su-

valsartan (2001), candesartan (CHARM-Alternative 2003, CHARM-Added, 2023), losartan again (HEAAL, 2012), and to a lesser extent telmisartan (1999, 2010) were evaluated in "systolic" HF trials, while candesartan (CHARM-Preserved, 2003) and irbesartan (2008) were appraised in HF with preserved systolic function trials[114–121]. European HF guidelines (2021) do not claim any preference for ACEs or ARBs, recommending them both as an alternative (IA). American guidelines (2022) prefer ACEs as the first choice in RAAS-naive patients[46,105].

The use of ARBs in the treatment of HF with reduced ejection fraction (HFrEF) has been upgraded recently by neprilysin inhibition which fits neatly with the neurohormonal concept of HF[122]. In PARADIGM-HF Trial (2014) the dual-acting angiotensin receptor-neprilysin inhibitor (ARNI) sacubitril valsartan reduced the composite endpoint of HF hospitalization and death in comparison with standard enalapril treatment[123,124]. ARNI therapy now has a class I indication for the treatment of patients with HFrEF[46,105,125].

The evolutionarily highly conserved family of natriuretic peptides comprises the atrial, brain, and C-type peptides (ANP, BNP, and CNP). ANP and BNP, secreted by the atria and ventricles, operate via the natriuretic peptide receptors type A (NPR-A) and type B (NPR-B), which are coupled to guanyl cyclase, mediating biological effects. Those include vasodilatation, natriuresis, and diuresis, inhibition of the RAAS, endothelin, and vasopressin, along with lipid mobilization. ANP is degraded rapidly by endopeptidase neprilysin. The inhibition of neprilysin increases the levels of ANP in circulation, with beneficial effects in HF[122,126,127].

Mechanistic reasoning may turn out to be overly simplistic when faced with the complexity of clinical medicine. Promising concepts may not work in clinical practice. Clinical trials may dash hopes placed in promising treatments. Nesiritide, a human recombinant B-type natriuretic peptide (BNP) with vasodilatory properties, binds to receptors in the vasculature, kidney, and other organs to mimic the actions of endogenous natriuretic peptides. It was approved by the FDA in 2001 for use in patients with acute HF based on studies showing hemodynamic and symptomatic improvements. A few years after its approval (2005), nesiritide fell out of use because small studies seemed to indicate an increased risk of kidney problems and an increased death rate. The ASCEND-HF study (2011) showed no impact of nesiritide on death or HF hospitalization[128–132].

Elevated resting heart rate has been linked to poor outcomes in patients with chronic systolic HF. Ivabradine may be added to neurohormonal treatments as the adjunctive therapy for HF with reduced ejection fraction (HFrEF) to slow sinus rhythm. It inhibits "funny" pacemaker current (I_f) of the sinoatrial node, not affecting the AV node, inotropy, diastolic function, cardiac output, vascular resistance, or blood pressure[133,134]. Ivabradine should be considered (IIa indication) in the patients with LVEF ≤35% in sinus rhythm and with a resting heart rate ≥70 bpm who remain symptomatic despite optimally up-titrated BBs, ACEi/ARNI, and MRA based treatment (or in BB intolerant patients) to reduce the risk of HF hospitalization and cardiovascular death[46]. Ivabradine is not a substitute for BBs[133].

Neurohormonal activation is the crucial mechanism underlying the progression of HF, and therapeutic antagonism of neurohormonal systems has become the cornerstone of

stava je postao temelj farmakoterapije HF. Shvaćanje HF se promijenilo: više se ne doživljava kao terminalni sindrom s beznadnom prognozom, nego kao izlječiv poremećaj[92].

Nije se, međutim, mogla zanemariti činjenica da je neurohormonalna inhibicija neučinkovita u HFpEF-u, tj. bar u polovice svih oboljelih od HF-a. Udio HFpEF-a porastao je na >50 %, prije svega zbog starenja populacije. Tipičan su fenotip pretile starije gospođe s malim, dobro kontraktilnim LV-om, dijabetesom, hipertenzijom i fibrilacijom atrija[77,135]. Dijastolička disfunkcija LV-a čimbenik je rizika, ali ne i glavni uzrok HFpEF-a. Prijelomna istraživanja HF-a s RAAS antagonistima i BB-om isključila su bolesnike s EF LV ≥40 %. Istraživanja s kandesartanom, irbesartanom i spironolaktonom specifično planirana za bolesnike s EF LV ≥40 % postigla su razočaravajuće rezultate. Istraživanje *CHARM-Preserved* (2003.) s kandesartanom pokazalo je samo umjereno smanjenje bolničkih prijema u bolesnika s EF LV >40 %, a istraživanje *I-PRESERVE* (2008.) s irbesartanom bilo je neutralno u pogledu ishoda bolesnika s HF-om i EF LV ≥45 %. Istraživanje *TOPCAT* (2014.) pokazalo je da u bolesnika s EF LV ≥45 % liječenje spironolaktonom nije znatno smanjilo zajednički ishod od CV smrti, HF-a i hospitalizacije[120,121,136].

Neučinkovitost nerohormonalne inhibicije u liječenju HFpEF-a zatekla je kardiološku javnost jer prognoza HFpEF-a može biti jednako ozbiljna kao ona HFrEF[137]. Kardiolozi su se osjećali bespomoćno jer je velika populacija bolesnika s HFpEF-om ostala bez ikakve strategije liječenja. Oprezna primjena diuretika za dekongestiju bila je jedina preostala terapijska mogućnost uz liječenje komorbiditeta[138,139]. HFpEF je fenotipski i patofiziološki raznolik poremećaj u kojemu bi terapija trebala ciljati uzročni fenotip i komorbiditete, ali je takav pristup bio frustrirajuće kompleksan[140]. Oslanjanje na špekulativno liječenje dijastoličke disfunkcije temeljeno na hemodinamskim pretpostavkama nije pomagalo. Morale su se tražiti nove strategije liječenja.

Razdjelnica za HFpEF od 40 do 4 5 % postavljena je da se razluči HFpEF od HFrEF-a ranijih istraživanja o HF-u. Međutim, istraživanja kao *CHARM-Preserved* i *TOPCAT* upućivala su na to da postoji prijelazna EF u rasponu 41 – 49 % gdje su povoljni učinci kandesartana i spironolaktona bili bolji nego s EF ≥50 %, premda ne tako dobri kao u bolesnika s EF-om <40 % u istraživanjima kod HFrEF-a. Pojam HF srednjeg raspona EF-a 40 – 49 % uveden je (≈2014.) i uskoro (2021.) preimenovan u HF s blago reduciranom EF (41 – 49 %) ili HFmrEF. To je međukategorija između HFrEF-a i HFpEF-a s procjenom prevalencije na 10 – 20 % od svih bolesnika s HFom. Europske su smjernice za HF 2021. ustvrdile: „premda se ne mogu dati čvrste preporuke za taj fenotip HF-a, ACE inhibitori, ARB, MRA, BB i ARNI mogu se razmotriti za smanjenje rizika od smrti i hospitalizacije zbog HF-a u bolesnika s HFmrEF (IIb)". Drugim riječima, neurohormonalna inhibicija može biti korisna u HFmrEF-u bolesnika, ali ne toliko kao u HFrEF bolesnika jer su dokazi mnogo slabiji[46,139–143]. Ažurirani dodatak Smjernicama ESC-a za HF iz 2023. dodaje dapagliflozin ili empagliflozin kao terapiju prvog izbora navodeći da se neurohormonalni inhibitori, koje čine skupine lijekova ACEI/ARNI/ARB, BB i MRA, mogu se razmotriti (II. b indikacija) u liječenju bolesnika s HFmrEF-om, dok su diuretici zbog nakupljanja tekućine i dapagliflozin/empagliflozin indicirani uz razinu preporuke I[125].

Dva osebujna neneurohormonalna lijeka pobudila su nade za liječenje HFrEF-a bolesnika u dodatku stanardnoj neuro-

pharmacotherapy for HF. The perception of HF has changed: it is no longer regarded as a terminal syndrome with a dismal prognosis but as a treatable disorder[92].

However, it was not possible to ignore the fact that neurohormonal inhibition did not work in patients with HFpEF, representing at least a half of all patients with HF. Their share has risen to >50%, owing mostly to the aging of the population. The typical phenotype are obese elderly women with a small, well-contracting left ventricle, diabetes, hypertension, and atrial fibrillation[77,135]. Diastolic left ventricular dysfunction is a risk factor but not the main cause of HF. Landmark HF studies with RAAS antagonists and BBs excluded patients with LV EF ≥40%. Trials with candesartan, irbesartan, and spironolactone, designed to explicitly address the efficacy of RAAS antagonists in patients with EF ≥40%, yielded disappointing results. The CHARM-Preserved trial with candesartan (2003) showed only a moderate reduction in hospital admissions among patients with HF with LVEF >40%. The I-PRESERVE trial (2008) with irbesartan was neutral about outcomes in patients with HF with LVEF ≥45%. The TOPCAT trial (2014) demonstrated that in patients with HF and LVEF ≥45%, the treatment with spironolactone did not significantly reduce the incidence of the primary composite outcome of cardiovascular death, aborted cardiac arrest, or hospitalisation[120,121,136].

Failure of neurohormonal inhibition to improve HFpEF took the cardiac community aback since the prognosis of HFpEF may be as grave as that of HFrEF[137]. Cardiologists were at a loss since a huge population of patients with HFpEF was left without any treatment strategy. Judicious use of diuretics for decongestion was the only treatment remaining, along with the treatment of comorbidities[138,139]. HFpEF is a phenotypically and pathophysiologically heterogeneous disorder in which therapy should target the underlying phenotypes, etiologies, and comorbidities, but such an approach was frustratingly complex[140]. Relying on speculative treatment of LV diastolic dysfunction based on hemodynamics did not help. New treatment strategies were needed.

The cut-off point for HFpEF of 40-45% was set to distinguish HFpEF from HFrEF of earlier HF trials. However, trials like CHARM-Preserved and TOPCAT indicated the presence of a transitional EF range from 40% to 49% where the beneficial effects of candesartan and spironolactone were better than with EF ≥50%, albeit not as good as with <40%. The term HF mid-range EF (40-49%) was introduced (≈2014) and soon (2021) renamed to HF with mildly reduced EF (41-49%) or HFmrEF. It is an intermediate category between HFrEF and HFpEF with an estimated prevalence of 10% to 20% among all patients with HF. The 2021 ESC guidelines on HF stated that "although no strong recommendations for this HF phenotypes can be made ACEIs, ARBs, MRAs, BBs, and ARNI can be considered to reduce the risk of death and HF hospitalization in HFmEF (IIb)". In other words, pharmacological neurohormonal inhibition may be beneficial in patients with HFmEF, but not as much as in patients with HFrEF, since the evidence is far weaker[46,139–143]. According to the 2023 ESC HF guidelines update, neurohormonal inhibitors comprising ACEI/ARNI/ARBs, BBs, and MRAs may be considered (class IIb recommendation) in patients with HFmrEF, while diuretics for fluid retention and dapagliflozin/empagliflozin are indicated with class I recommendation[125].

Two peculiar new non-neurohormonal drugs have raised hopes for the treatment of patients with HFrEF in addition to the standard neurohormonal inhibition. Vericiguat works via stimulation of soluble guanylate cyclase (sGC) in the NO-sGC-

hormonalnoj inhibiciji. Vericiguat djeluje stimulacijom topljive guanilat ciklaze (sGC) u NO-sGC-cGMP molekularnom putu potičući funkcionalnost miokarda i vazodilataciju[144]. Aktivator srčanog miozina omekamtiv mekarbil koji pojačava djelovanje miozina na aktin s pozitivnom inotropijom. Za oba je lijeka dokazano (vericiguat u istraživanju *VICTORIA*; omekamtiv mekarbil u istraživanju *GALACTIC-HF*) da smanjuju skupni rizik od CV smrti i hospitalizacije u bolesnika s HFrEF-om [55,56,145–147].

HIPOTEZA STANIČNOG OPTEREĆENJA

Hipoteza staničnog opterećenja (2019. –) zadnja je koncepcija patofiziologije HF-a što ju je predložio M. Packer. Ispunila je znatne praznine u razumijevanju HF-a koje su ostale u neurohormonalnoj i ranijim hipotezama. Nadahnuta je pojavom SGLT2 inhibitora kao prekretnicom. Bit je da stanična disfunkcija potiče HF. Još su jednom slučajna zapažanja, klinička praksa i klinički pokusi utirali stazu napretka.

Natrij-glukoza suprijenosnici (kotransporteri) SGLT1 i SGLT2 posrednici su epitelnoga prijenosa glukoze. Dok je SGLT1 bitan za većinu dijetalnog preuzimanja glukoze u crijevu, SGLT2 je ključan za vraćanje glukoze u bubrežnom tubularnom sustavu. Lijekovi koji inhibiraju SGLT2 završavaju nastavkom „flozin". Prototip florizin izoliran je u kori korijena drveća već 1835. Premda nije imao medicinsku primjenu, njegovi su hipoglikemički i glukozurički učinci opisani već 1886. Tek nedavno (2012.) uveden je dapagliflozin kao antidijabetik. SGLT2i reguliraju skupni prijenos glukoze i natrija u nefronu, inhibirajući preuzimanje glukoze, potičući glukozuriju i snizujući razinu glukoze u serumu. Na neki način SGLT2i djeluju kao diuretici, potičući osmotsku diurezu, zajedno s glukozurijom i natriurezom. U usporedbi s placebom, SGLT2i snizuju razinu HbA1c u prosjeku za 0,5 – 0,8 % ako se primjenjuje u monoterapiji, ili u dodatku drugim antidijabeticima (zajedno sa skromnim gubitkom na težini). Antidijabetički učinak, kao primarna namjena, bio je skroman, ali su se SGLT2i iskazali blagotvornim učincima na srce i bubrege[148–151].

Uzbuna izazvana rosiglitazonom, za koji se u postmarketinškom nadzoru ustanovilo da povećava CV smrtnost, urodila je zahtjevom da se svi novi antidijabetici moraju podvrgnuti kliničkim istraživanjima CV ishoda prije nego ih odobri FDA. To je potaknulo provođenje istraživanja *EMPA-REG OUTCOME* koje je neočekivano otkrilo znatno smanjenje primarnoga zajedničkog ishoda od CV smrti, preživjelog infarkta miokarda i moždanog udara u skupini ispitanika liječenih empagliflozinom[152]. Slučajno sretno otkriće potaknulo je nekoliko drugih istraživanja s CV ishodima, uključujući *CANVAS* (kanagliflozin, 2017.) i *DECLARE-TIMI* (dapagliflozin, 2019.) koji su pokazali da su povoljni rezultati svojstveni čitavoj skupini inhibitora SGLT2 receptora. Rizik od hospitalizacije zbog HF-a bio smanjen u bolesnika s anamnestičkim podatcima o HF, ali i u onih bez nje. S obzirom na to da su povoljni učinci postignuti unutar dva mjeseca, nisu pripisani regulaciji dijabetesa nego o njoj neovisnim učincima[153,154]. Štoviše, opaženi su i izrazito povoljni učinci na kroničnu bubrežnu bolest[155–157].

Četiri prijelomna istraživanja (dva za HFrEF i dva za HFpEF) postavila su standard liječenja HF-a s najjačom (IA) preporukom za primjenu SGLT2i u cijelom rasponu EF-a (HFrEF, HFmrEF, HFpEF) prema smjernicama za HF[105,125]. To su sljedeća istraživanja: *DAPA HF* (dapagliflozin, 2019.), *EMPEROR REDUCED* (empagliflozin, 2020.), *EMPEROR PRESER-*

cGMP pathway, with resulting improvements in myocardial function and vasodilation[144]. The cardiac myosin activator omecamtiv mecarbil, which potentiates the effects of myosin on actin, exerts positive inotropic effects. Both drugs reduced the composite endpoint of cardiovascular death and hospitalization in HFrEF trials, vericiguat in VICTORIA and omecamtiv mecarbil in GALACTIC-HF[55,56,145–147].

THE CELLULAR STRESS HYPOTHESIS

The cellular stress hypothesis (2019-) is the final concept of HF pathophysiology proposed by M. Packer. It filled the substantial gaps in the understanding of HF left by the neurohormonal and the previous hypotheses. It has been inspired by the "game changer" role of SGLT2 inhibitors (SGLT2is). The essence is that cellular dysfunction perpetuates chronic HF. Once again, chance observations, clinical practice, and trials led the way.

Sodium-glucose cotransporters SGLT1 and SGLT2 are mediators of epithelial glucose transport. While SGLT1 accounts for most of the dietary glucose uptake in the intestine, SGLT2 is accountable for the majority of glucose reuptake in the tubular system of the kidney. The medications that inhibit SGLT2 suffix with flozins. The prototype phlorizin was identified in root bark from trees as early as in 1835. Although phlorizin did not show any obvious medicinal value, its blood glucose-lowering and glucosuric effects were described as early as 1886. Only recently (2012) was dapagliflozin introduced as antidiabetic drug. SGLT2is modulate the sodium-glucose cotransporter on the nephron, inhibiting glucose reuptake, inducing glucosuria, and lowering the serum glucose levels. In a way, SGLT2is act as diuretics stimulating osmotic diuresis along with glucosuria and natriuresis. Compared with placebo, SGLT2is reduce HbA1c levels by an average of 0.5-0.8% when used as monotherapy or add-on therapy (along with a modest weight loss). As antidiabetic agents, which was the primary indication, SGLT2is are modestly effective, but they proved to be exceptional in cardiac and renal protection[148–151].

The stir caused by rosiglitazone, which was found to increase cardiovascular mortality in post-marketing surveillance, required that new antidiabetic drugs undergo cardiovascular outcome trials prior to FDA approval. This led to the EMPA-REG OUTCOME empagliflozin trial (2015) which unexpectedly revealed a significant reduction in primary composite outcomes of cardiovascular death, nonfatal myocardial infarction, and stroke in the treatment group[152]. The serendipitous discovery led to several landmark confirmatory trials on cardiovascular outcomes including CANVAS (canagliflozin, 2017) and DECLARE-TIMI (dapagliflozin, 2019), with positive results, indicating that the favorable outcomes were attributable to a class effect of SGLT2 receptor inhibition. The risk of HF hospitalization was reduced in patients with and without HF history. As the benefits were observed already within 2 months, they were not attributed to the regulation of diabetes but to independent effects of SGLT2i[153,154]. Moreover, marked beneficial effects on chronic kidney disease were also observed[155–157].

Four landmark trials (two for HFrEF and two for HFpEF) set the standard for HF treatment, establishing the strongest (IA) recommendations for SGLT2is use across the whole EF range (HFrEF, HFmrEF, HFpEF) in HF guidelines (2022)[105,125]. Those trials were: DAPA-HF (dapagliflozin 2019), EMPEROR

VED (empagliflozin, 2021.) i *DELIVER* (dapagliflozin, 2022.). Rezultati za dapagliflozin i empagliflozin bili su sukladni: smanjenje skupnog rizika od CV smrti i hospitalizacije zbog HF-a za gotovo 20%[158–161].

Slučajno otkriće koje je skromnu skupinu antidijabetičkih lijekova promoviralo u prekretnicu liječenja HF-a uzbudilo je, ali i zateklo kardiološku javnost. Eksperimentalna su istraživanja ponudila mnoga objašnjenja, većinom temeljena na citoprotekciji. SGLT2i postižu citoprotektivne učinke na bolesno srce neovisno o natrij-glukoza prijenosnom sustavu potičući signaliziranje koje oponaša staničnu nutritivnu oskudicu i autofagično razgrađivanje. Konačni su ishodi stanično rasterećenje, revitalizacija mitohondrija, potiskivanje upalnog signaliziranja i apoptoze[162].

U bujici podataka o staničnim učincima SGLT2i jedva je moguće sažeto ocrtati sjedinjujuću koncepciju. Možda je tomu najbliža hipoteza da SGLT2i čuvaju srce i bubrege mimikrijom gladovanja preko aktivacije staničnih senzora energijske nestašice, neovisno o SGLT2 proteinu. Takvo stanje potiče SIRT1/AMPK, a potiskuje Akt/mTOR signaliziranje, smanjuje oksidativni stres, normalizira strukturu i funkciju mitohondrija, suzbija upalu, ublažuje koronarnu mikrovaskularnu ozljedu, jača kontrakciju i čuva miokard. SGLT2i pospješuju autofagiju neovisno o učincima na glukozu. Potiču staničnu produkciju ATP-a i sintezu hemoglobina povećanjem sadržaja reaktivnog Fe^{2+} u citosolu uz smanjenje razina hepcidina i feritina. Time se ublažuje funkcionalni manjak željeza nastao u inflamatornom miljeu HF[156,162,163].

U dekompenziranom srcu stanična je razina proteina koji prenosi glukozu kroz staničnu membranu tipa 1 (GLUT1) povišena, zajedno s prekomjernom glikolizom i manjkavom oksidacijom glukoze, uzrokujući nakupljanje štetnih metabolita glukoze koji potiču mTOR i potiskuju signaliziranje oskudice nutrijenata. Preuzimanje masnih kiselina dugog lanca raste, ali im je oksidacija manjkava, što remeti stvaranje ATP-a i uzrokuje nakupljanje toksičnih lipidnih metabolita u citosolu. Stanje se pogoršava disfunkcijom mitohondrija i signaliziranja oskudice nutrijenata. Posljedično nakupljanje aminokiselina aktivira mTOR. SGLT2i liječe abnormalnosti u metabolizmu glukoze i masnih kiselina dugog lanca inhibicijom GLUT1, stimulacijom signaliziranja manjka nutrijenata i oporavkom vitalnosti mitohondrija. Time se popravljaju oksidacija nutrijenata i oksidativna fosforilacija te priječi nakupljanje štetnih nusprodukata glukoze i lipida u citosolu[162,163].

Za HF je bitan raspored nakupljene tekućine. SGLT2i mogu drukčije od diuretika Henleove petlje regulirati odnos intersticijskog i intravaskularnog odjeljka. U kongestivnom HF-u intersticijski su edemi glavni znak bolesti. SGLT2i mogu ciljano smanjiti intersticijski volumen uz neznatnu promjenu intravaskularnog volumena, dok diuretici Henleove petlje reduciraju oba. Pretpostavlja se da nejednaka regulacija volumena djelovanjem SGLT2i suzbija štetnu neurohormonalnu stimulaciju koja nastaje zbog gubitka intravaskularnog volumena[153].

Nameće se presudno pitanje kako SGLT2i funkcioniraju u HFpEF-u. Odgovor je složen i odražava fenotipsku raznolikost HFpEF i zamršenost SGLT2i djelovanja. Mnogi su dijelovi ove slagalice složeni, pri čemu je uočljivo znatno preklapanje HFpEF-a i HFrEF-a. Pokazalo se da SGLT2i potiču uzorak transkripcijskog odgovora na stanično izgladnjivanje i hipoksiju, s porastom ketoze, eritropoetina i autofagičnog raz-

REDUCED (empagliflozin 2020), EMPEROR PRESERVED (empagliflozin 2021), and DELIVER (dapagliflozin 2022). The results for dapagliflozin and empagliflozin were highly congruent: both reduced the composite endpoint of cardiovascular death and HF hospitalization by nearly 20%[158–161].

The chance discovery which promoted the modest class of antidiabetic agents to a game changer in HF treatment stirred excitement but also took the cardiac community aback. The mechanisms behind the phenomenon were shrouded in mystery. The upheaval among clinical cardiologists stimulated a huge research effort to provide scientific explanations for the mechanisms of action. Experimental research proposed many explanations, mostly related to cytoprotection. SGLT2is exert cytoprotective effects on the failing heart via SGLT2-independent pathways to increase nutrient-deprivation signaling and autophagic flux, thus reducing cellular stress, improving mitochondrial vitality, and suppressing inflammatory signaling and apoptosis[162].

In the surge of data on the cellular effects of SGLT2, it is hardly possible to concisely outline a unifying concept. Perhaps closest to it is the hypothesis that SGLT2s provide cardiac and renal protection by inducing a state of fasting mimicry through the activation of low-energy sensors, which is not mediated through the SGLT2 protein. This state activates SIRT1/AMPK and suppresses Akt/mTOR signaling, which lead to a reduction in oxidative stress, normalized mitochondrial structure and function, suppression of inflammation, minimization of coronary microvascular injury, enhanced contractile performance, and myocardial protection. SGLT2is promote autophagy, independent of their effects on glucose. SGLT2is might enhance ATP and hemoglobin production by expanding the pool of reactive cytosolic Fe^{2+}. This is due to SGLT2i-induced decline in hepcidin and ferritin levels. which alleviates functional iron deficit mediated by the HF inflammatory milieu[156,162,163].

In the failing heart, glucose transporter type 1 (GLUT1) levels are upregulated, along with excessive glycolysis and defective glucose oxidation, causing cytosolic accumulation of injurious glucose intermediates that activate mTOR and suppress nutrient-deprivation signaling. The uptake of long-chain fatty acids rises, but their oxidation is defective, impairing ATP production and causing cytosolic accumulation of toxic lipid intermediates, worsened by mitochondrial and nutrient-deprivation signaling dysfunction. The ensuing cytosolic accumulation of amino acids activates mTOR. SGLT2is cure the abnormalities in glucose, long-chain fatty acid, and amino acid metabolism by inhibiting GLUT1, stimulating nutrient-deprivation signaling, and restoring mitochondrial vitality. This improves nutrient oxidation and oxidative phosphorylation, preventing cytosolic accumulation of harmful glucose and lipid by-products[162,163].

With regard to HF, fluid accumulation pattern is critical. SGLT2is may differentially regulate the interstitial vs. intravascular compartment when compared with loop diuretics. In congestive HF, interstitial edema is the hallmark of disease. SGLT2 inhibitors may selectively reduce interstitial volume with minimal change in blood volume, whereas loop diuretics reduce both interstitial and intravascular volume. It has been assumed that this differential volume regulation by SGLT2is (interstitial > intravascular) may limit the aberrant reflex neurohormonal stimulation induced by intravascular volume depletion[153].

The crucial question arises how SGLT2is work in HFpEF. The answer is complex, reflecting the heterogeneity of HFpEF phenotypes and the intricacy of SGLT2i actions. Many pieces of

građivanja, uz promjenu ravnoteže iona željeza, što sve može popraviti srčanu energetiku i funkciju. Ovi lijekovi također reduciraju epikardno masno tkivo i podešavaju adipokinsko signaliziranje slabeći upalu i oksidativni stres. SGLT21 mogu utjecati na ionsku homeostazu u srčanim miocitima. Nakraju, pokazalo se da smanjuju krutost miofilamenata i fibrozno remodeliranje izvanstaničnog matriksa srca s poboljšanjem dijastoličke funkcije. Od istraživanja se očekuje da unaprijede i razumijevanje i liječenje HF-a[164].

Ključna poruka istraživanja s SGLT2i jest da je stanično opterećenje, neprepoznato u ranijim teorijama, bitno za patofiziologiju HF-a. Potraga za učinkovitim liječenjem bila je glavni pokretač evolucije teorijskih koncepata. Nova koncepcija ne odbacuje, nego revidira ranije napretkom strategije liječenja.

Suvremeno liječenje HFrEF-a, a dijelom i HFmEF-a temelji se na četirima stupovima (osim diuretika): 1) ACE inhibitori/ARB/ARNI, 2) BB, 3) MRA i 4) SGLT2i (redoslijed je kronološki). Liječenje HFpEF-a, osim sveprisutnih diuretika, temelji se na SGLT2i koji čine EF irelevantnom. Četverostruka terapija ARNI kombinacijom, BB, MRA i SGLT2i uspostavljena je kao liječenje prvog izbora u bolesnika s HFrEF-om prema smjernicama za HF. Sve je više podataka da takvo liječenje koristi i mnogim bolesnicima s EF-om >40 %. SGLT2i su korisni bez obzira na EF. Liječenje HFpEF-a trebalo bi se provoditi ciljano prema uzročnom fenotipu, komorbiditetu i etiologiji. Hipertenzivni fenotip često zahtijeva ACE inhibitor, ARB, BB, a nerijetko i MRA, neovisno o očuvanoj EF, čineći nejasnim kontrast između HFpEF-a i HFrEF-a. Pretili bolesnici, osobito dijabetičari, mogu dobro iskoristiti agoniste GLP1 receptora, u dodatku SGLT2i[140,165].

U kliničkoj praksi mogu se opaziti određene nedosljednosti u uporabi antagonista receptora aldosterona u bolesnika s HFpEF-om. Smjernice ih izrijekom ne preporučuju, ali i ne osporavaju. Nadopuna ESC smjernica 2023. osvrće se na to pitanje jer su mnogi bolesnici s HFpEF-om u istraživanjima s SGLT2 primali lijekove iz skupine MRA i druge neurohormonalne inhibitore. Istraživanje *TOPCAT* sa spironolaktonom iskazalo je neutralne sveukupne rezultate, ali s dvojbama u tumačenju zbog izrazitih regionalnih razlika u selekciji bolesnika. Malo istraživanje (*RAAM-PEF*, 2011.) pokazalo je da je primjena epleronona u bolesnika s HFpEF-om bila povezana sa znatnim smanjenjem biljega optjecaja kolagena i poboljšanjem dijastoličke funkcije. Stoga ima smisla propisati lijek MRA skupine zajedno s diuretikom Henleove petlje u bolesnika s HFpEF-om[125,166,167].

Novi entitet nazvan HF-om s oporavljenom (ili poboljšanom) istinom frakcijom nedavno je prepoznat, zajedno s nedoumicama o prognozi i liječenju[168–171]. Podatci istraživanja *DELIVER* pokazuju da su SGLT2i korisni u takvih bolesnika[161].

Spoznaja da miokard u HF-u ponavlja program fetalnog signaliziranja općeprihvaćena je, a nedavno revidirana i osnažena. Reaktivacija fetalne beta-izoforme teškog lanca miozina koja zamjenjuje zrelu alfa-izoformu i prelazak s masnih kiselina na glukozu kao glavno „gorivo" u miocitima dekompenziranog srca dobro su poznati primjeri. Fetalno je reprogramiranje kratkoročna adaptacija koja postaje dugoročno pogubna[172].

Molekula uridin difosfat N-acetilglukozamina (UDP-GlcNAc) nedavno je prepoznata kao čvorište fetalnog reprogramiranja u dekompenziranom srcu. Trajno povećanje preuzimanja glukoze u preopterećene srčane miocite, osobito uz

this jigsaw puzzle have been put together, noting the considerable overlapping between HFpEF and HFrEF. SGLT2is have been shown to induce a nutrient-deprivation and hypoxic-like transcriptional paradigm, with increased ketosis, erythropoietin, and autophagic flux in addition to altering iron homeostasis, which may improve cardiac energetics and function. These agents also reduce epicardial adipose tissue and modify adipokine signaling attenuating inflammation and oxidative stress. SGLT2is may affect cardiomyocyte ionic homeostasis. Finally, they have been shown to reduce myofilament stiffness as well as extracellular matrix remodeling/fibrosis in the heart, improving diastolic function. The research on the salutary mechanisms of SGLT2is in HFpEF is expected to improve both the understanding of HFpEF and its treatment[164].

The key-message from SGLT2i trials is that cellular stress, unrecognized in previous concepts, is essential for HF pathophysiology. The quest for efficient treatments was the main driver behind this evolution of concepts. The new concept did not repeal but instead revised the previous ones, improving treatment strategies.

Modern HFrEF and partly HFmrEF treatments are based on four pillars (besides diuretics): 1) ACEIs or ARBs, preferably in ARNI combination, 2) BBs, 3) MRAs, and 4) SGLT2is (listed chronologically). With regard to HFpEF, besides omnipresent diuretics, there are SGLT2is which span the entire EF spectrum, rendering EF irrelevant. Quadruple therapy with ARNI, BB, MRAs, and SGLT2is has been established as first-line therapy for patients with HFrEF in current HF guidelines. There is increasing evidence that many patients with HF with an LVEF >40% may benefit from these medications. SGLT2is are beneficial regardless of ejection fraction. HFpEF treatment should be targeted according to the underlying phenotype, comorbidities ant etiology. The hypertensive phenotype often requires ACEIs, ARBs, BBs, and not rarely MRAs, irrespectively of preserved EF, blurring the distinction between HFrEF and HFpEF. Obese and diabetic phenotypes may benefit greatly from GLP1 receptor agonists, in addition to SGLT2i[140,165].

Some inconsistencies may be observed in clinical practice with regard to the use of MRAs in patients with HFpEF. The guidelines neither recommend the use of MRAs in those patients, nor oppose it. The question has been addressed in the 2023 update, since many patients with HFpEF who benefited from SGLT2i received MRAs and other neurohormonal inhibitors. The TOPCAT trial with spironolactone found generally neutral results but with ambiguity in interpretation due to marked regional differences in patient selection. A small trial (RAAM-PEF, 2011) demonstrated that the use of epleronone in patients with HFpEF was associated with significant reduction in markers of collagen turnover and improvement in diastolic function. Thus, it may make sense to prescribe a MRA drug along with a loop diuretic in patients with HFpEF[125,166,167].

A new entity called HF with recovered (or improved) ejection fraction (HFrecEF) has been recently recognized, along with uncertainties about prognosis and treatment[168–171]. The data from the DELIVER trial indicate that these patients benefit from SGLT2 inhibition[161].

The idea that the failing myocardium recapitulates the fetal signaling program has been generally accepted but has been recently revisited and reinvigorated. The reactivation of fetal beta-myosin heavy chain isoform replacing the mature α variant and the shift from fatty acids to glucose as the main "fuel"

oslabljeno SIRT1 i AMPK signaliziranje, pojačava biosintezu heksozamina. Njezin konačni proizvod, UDP-GlcNAc, bitan je senzor suviška hranjivih tvari. UDP-GlcNAc je ključan za O-GlcNAcilaciju koja u sudioništvu s mTOR fosforilacijom brzo i nepopravljivo mijenja mnoštvo proteina u jezgri, citoplazmi i mitohondrijima. Pogubne su posljedice poremećaj kinetike kalcija s kontraktilnom disfunkcijom, aritmijama povezanima s aktivacijom naponski reguliranih kalcijevih kanala i Ca^{2+}/CaMKII, disfunkcijom mitohondrija, maladaptacijskom hipertrofijom, fibrozom i HF-om. Šteta se može spriječiti utišavanjem O-GlcNAcilacije koja znači izazov za inovacije, uključujući mRNA tehnologije[173].

Očito je HF raznorodan poremećaj koji izmiče sjedinjujućim koncepcijama i terapijskim pristupima. Istisna je frakcija tek nesavršeno sredstvo razlučivanja fenotipa i strategija liječenja[174]. Hipoteza staničnog opterećenja sagledava zajedničke nazivnike u staničnim poremećajima. Pobuđuje nadanja da će eksperimentalna znanost razviti nove lijekove.

Nažalost, iskustvo stranputica podučava da je razočaranje pratilac nade. Pozitivni inotropni lijekovi i neseritid zorni se primjeri. Monoklonska protutijela usmjerena protiv faktora tumorske nekroze α (TNFα) etanercept i infliksimab pobudila su velike nade u liječenju HF-a temeljenog na suzbijanju pogubnoga upalnog odgovora i štetnog remodeliranja miokarda. Klinička istraživanja *RECOVER*, *RENNESAINCE* i *ATTACH* ugasila su, međutim, takve nade (2001.)[175,176].

Zaključne napomene

Preostaje sažeti razvoj shvaćanja o HF-u počevši od priprostih kliničkih predodžbi do teze o višeuzročnom multiorganskom poremećaju. Motrišta su evoluirala od iskustvenog tumačenja kliničkih simptoma i znakova, preko cjelovitog pristupa s mjerenjima i slikovnim prikazima, sve do suptilne analize na staničnoj razini. Osler je sagledavao HF kao krajnji dekompenzirani stadij raznih srčanih bolesti. Dijagnoza se temeljila samo na kliničkim simptomima i znakovima. Takav tradicionalan pristup prevladavao je sve do 70-ih godina prošloga stoljeća, kad su dijagnostičke metode strukturnog i funkcionalnog prikaza srca i krvnih žila omogućile hemodinamsku analizu. Potkraj stoljeća neurohormonalna je hipoteza potaknula napredak laboratorijske dijagnostike. To je urodilo i razvojem analize vrijednosti NT-pro-BNP-a koja je omogućila rano prepoznavanje i praćenje HF-a. Težina simptoma običavala se stupnjevati funkcionalnim NYHA razredima I. – IV. A-B-C-D stupnjevanje HF-a uvedeno je u SAD-u 2001. Ono sagledava razvoj HF-a od rizičnih čimbenika (A), preko asimptomatskih (B) i simptomatskih (C) strukturnih promjena srca do refraktornoga završnog stadija HF-a (D). Europske se smjernice ne koriste takvim simboličkim nabrajanjem, ali također cjelovito opisuju tijek HF-a od rizičnih čimbenika do uznapredovanoga stadija. Takav se pogled suprotstavlja nekadašnjoj predodžbi o HF-u kao beznadnom stanju s edemima pogubnoga kliničkog tijeka[24,177,178].

Ovaj pregledni članak bio je usredotočen na patofiziološke koncepcije HF-a sukladno farmakološkom liječenju. Cjelovit pristup također obuhvaća druge aspekte, počevši od preventivnih mjera u načinu života. Naprave, poput srčane resinkronizacije, fiziološke elektrostimulacije i i implantabilnog defibrilatora (ICD) poboljšale su ishode povrh lijekova. Starija klinička istraživanja lijekova za HF provedena prije uvođenja ICD-a kao standarda liječenja, jedva da su usporediva s noviji-

in the myocytes of the failing heart are well-known examples. Fetal reprogramming is adaptive in the short time but is deleterious if sustained for long periods[172].

The uridine diphosphate N-acetylglucosamine (UDP-GlcNAc) molecule has been identified recently as a hub of fetal reprogramming in the failing heart. Prolonged increases in glucose uptake in overburdened cardiac myocytes, especially when SIRT1 and AMPK signaling is suppressed, enhances the hexosamine biosynthesis pathway. Its final product, UDP-GlcNAc, acts as a critical nutrient surplus sensor. UDP-GlcNAc is the key step for O-GlcNAcylation, which in collusion with mTOR-mediated phosphorylation rapidly and reversibly modifies a multitude of intracellular proteins in the nucleus, cytoplasm, and mitochondria. The deleterious effects are impaired calcium kinetics with contractile dysfunction, arrhythmias related to activation of voltage-gated sodium channels and Ca^{2+}/CaMKII, mitochondrial dysfunction, maladaptive hypertrophy, fibrosis, and HF. Damage can be prevented by muting of O-GlcNAcylation, which poses a challenge for innovations, including the use of m-RNA technologies[173].

It turns out that chronic HF is heterogeneous disorder defying unifying concepts and treatment approaches. Ejection fraction is only an imperfect tool to distinguish between the phenotypes with different treatment strategies[174]. The concept of cellular stress identifies common denominators at a cellular level. This raises hopes that experimental research will create new drugs based on this concept.

Unfortunately, the experience of previous blind alleys in research paths teaches that disappointment is a companion of hope. Positive inotropic agents and nesiritide are the examples. Monoclonal antibodies directed against tumor necrosis factor α (TNFα) etanercept and infliximab raised high hopes in the treatment of HF, considering the role of detrimental inflammatory response in the process of adverse myocardial remodeling. However, the clinical trials RECOVER, RENNESAINCE, and ATTACH dashed these hopes in 2001[175,176].

Concluding remarks

All that remains is to briefly comment on the evolving understanding of HF from simplistic clinical concepts to the thesis of a complex multicausal and multiorgan disorder. Viewpoints shifted from a mechanistic approach all the way down to the cellular level. Osler viewed HF as a terminal decompensated stage of many cardiac diseases. The diagnosis was based on clinical symptoms and signs alone. The traditional approach prevailed up to the 70s, when cardiac imaging provided hemodynamic quantitation. At the end of century, the neurohormonal concept stimulated the progress of laboratory diagnostics, leading to the launch of the NT-proBNP assay which enabled early recognition and monitoring of HF. Traditionally, the severity of symptoms was graded by NYHA functional classes from I to IV. The A-B-C-D HF staging was introduced in the USA in 2001. It describes the development of HF ranging from risk factors (A), structural heart disease without (B) and with prior or current failure symptoms (C), to refractory HF (D). European guidelines do not use such symbolic numeration but also describe the course of HF comprehensively, ranging from etiological factors to the advanced stage. Such a view contrasts with the historical notion of HF as a terminal edematous state with an ominous prognosis and detrimental clinical course[24,177,178].

ma. S druge strane, čini se da novi lijekovi za HF smanjuju korist od ICD-a smanjujući rizik od nagle aritmične smrti[179,180]. Revaskularizacija, kirurška ili perkutana, jedva da je pokazala korist u pogledu ishoda liječenja HF-a (HFrEF) uzrokovana ishemijskom bolesti srca. Mogla (ili trebala) bi se razmotriti u pažljivo odabranih bolesnika nakon analize pojedinačnih slučajeva[181–183]. Epigenetička modulacija, uključujući mRNA postupke, otvara novu perspektivu liječenja[184,185]. Regeneracijske strategije koje su budile zanos kardiološke zajednice prije dvaju desetljeća, a onda zamrle, nedavno su ponovno oživljene[186–190]. Suvremeni arsenal liječenja HF-a uključuje spektar pristupa sa staničnim lijekovima i srčanom transplantacijom na suprotnim polovima. Transplantacija srca, međutim, izuzetna je situacija i izlaz iz nužde, a lijekovi su uobičajena svakodnevnica.

Raznolikost pristupa liječenju odražava složenost patofiziologije HF-a, neispunjene ciljeve (HF je još pogubna bolest) i nedovoljno razumijevanje uzročnih mehanizama. Pokazalo se da je svođenje patofiziologije HF-a na disfunkciju srčane crpke i slabost bubrega da izluče višak zaostale izvanstanične tekućine odviše pojednostavnjena koncepcija za učinkovite strategije liječenja. Dopuna koncepcije hemodinamikom krvotoka nije mnogo pomogla; tako osmišljene terapijske intervencije postizale su samo prolazna poboljšanja, ali bez utjecaja na konačne ishode. Tek je prekretnica otkrićem da je čvorište patofiziologije HF-a poguban sistemski neurohormonalni odgovor dovela do odlučujućeg uspjeha u smanjenju smrtnosti i pobola farmakološkom neurohormonalnom inhibicijom. Ta terapija, međutim, nije imala učinka u HFpEF-u, što je razotkrilo nedostatke u razumijevanju. Slučajno otkriće SGLT2i koji su učinkoviti u HFpEF-u i kardiorenalnom sindromu osvijetlilo je stanične aspekte HF-a. Povratak analizi stanične patofiziologije dekompenziranog srca i povezanih organa, osobito bubrega, obećava pronalazak novih puteva liječenja HF-a. Sa stajališta eksperimentalnih istraživanja u kardiologiji, modulacija mitohondrijske funkcije može biti jedan od tih puteva[191–194].

This review focused on the pathophysiological concepts of HF in line with pharmacological management. A comprehensive approach includes other aspects, starting with preventive lifestyle changes. Devices, like cardiac resynchronization, physiological pacing, and implantable cardiac defibrillator (ICD), have improved clinical outcomes in addition to the drugs. Older outcome trials with HF drugs, conducted before the ICDs became a standard of care, are difficult to compare with the newer ones. Conversely, new HF treatments appear to reduce the benefit of ICD by decreasing the risk of sudden cardiac death[179,180]. Surgical or alternatively percutaneous revascularization has showed hardly any benefits on outcomes in the treatment of HF (HFrEF) due to ischemic heart disease. It may (or should) yet be considered in patients carefully selected on an individual basis[181–183]. Epigenetic modulation, including mRNA technologies, is offering new prospects for treatment[184,185]. Regenerative strategies, which caused enthusiasm in the cardiac community two decades ago but then stalled, have been recently revisited[186–190]. The modern armamentarium for HF treatment includes a gamut of approaches with cellular drugs and heart transplant at opposite sides of the spectrum. However, heart transplant is a bail-out action, while the drugs are the mainstay.

The diversity of treatment approaches reflects the complexity of HF pathophysiology, unmet needs (HF is still a detrimental disorder), and insufficient understanding of the underlying mechanisms. Reducing HF pathophysiology to the malfunction of the heart pump, with failure of the kidneys to excrete the excess of retained extracellular fluid, proved to be a simplistic concept insufficient for efficient treatment strategies. Adding the hemodynamics of circulation to the concept did not help much either; the resulting pharmacological interventions may have brought some temporary relief but without any impact on the final outcomes. Only a paradigm shift, discovering that the hub of HF pathophysiology is a detrimental systemic neurohormonal response, led to a breakthrough with reduction in adverse cardiovascular outcomes (including mortality) by pharmacological neurohormonal inhibition. HFpEF, where neurohormonal inhibition did not work, exposed the gaps in understanding. Chance discovery of SGLT2is, which are also beneficial for HFpEF and cardiorenal syndrome, highlighted the cellular aspects of HF. Revisiting cellular pathophysiology of the failing heart and the related organs, especially of the kidneys, holds promise to find new avenues of HF treatment. From the viewpoint of experimental research in cardiology, modulation of mitochondrial function may be one of those avenues[191–194].

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