EPIT-HF survey chronického srdcového zlyhávania s redukovanou, mid-range a zachovanou ejekčnou frakciou na Slovensku. 1. časť: Epidemiológia

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Abstrakt. *Pozadie:* Existuje limitovaný rozsah údajov o klinických charakteristikách a ich komparácii pri všetkých troch fenotypoch srdcového zlyhávania (SZ). Na Slovensku neboli publikované žiadne údaje o epidemiológii SZ s „mid-range" ejekčnou frakciou (HFmrEF).

Ciele: V prospektívnom prieskume určiť a porovnať epidemiologické charakteristiky troch fenotypov chronického SZ (SZ s redukovanou ejekčnou frakciou – HFrEF, SZ so zachovanou ejekčnou frakciou – HFpEF a HFmrEF).

Metodika: Prieskum EPIT-HF realizovalo 161 lekárov, z nich 115 kardiológov (71,4 %) a 46 internistov (28,6 %). Do prieskumu boli zahrnutí následní ambulantní pacienti s diagnózou chronického SZ starší ako 18 rokov. Na zaradenie neexistovali žiadne exklúzne kritériá. Fenotypy SZ sme stanovili podľa ejekčnej frakcie ĽK (EFĽK): HFrEF – EFĽK < 40 %, HFmrEF – EFĽK 40 – 49 %, HFpEF – EFĽK ≥ 50 %. Do prieskumu EPIT-HF sme zaradili 2 677 pacientov. Podsúbory HFrEF, HFmrEF a HFpEF tvorilo 1 169 (43,7 %), 720 (26,9 %), respektíve 788 (29,4 %) pacientov.

Výsledky: Zistili sme významné vzájomné rozdiely troch fenotypov SZ v zmysle demografie, etiológie, symptomatológie,

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EPIT-HF survey of chronic heart failure with reduced, mid-range and preserved ejection fraction in Slovakia. Part 1: Focus on epidemiology

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Abstract. *Background:* There is only a limited range of data on clinical characteristics of all three phenotypes of chronic heart failure (HF) and on their comparisons. Epidemiologic data on chronic heart failure with mid-range ejection fraction (HFmrEF) in Slovakia has not been published until yet.

Aims: In a prospective survey to determine and compare epidemiological characteristics of three phenotypes of chronic HF – heart failure with reduced ejection fraction (HFrEF), HFmrEF and heart failure with preserved ejection fraction (HFpEF).

Method: The survey was performed by 161 physicians, including 115 cardiologists (71.4%) and 46 internists (28.6%). Consecutive outpatients with a diagnosis of chronic HF aged at least 18 years were included. There were no exclusion criteria. The HF phenotypes were determined according to left ventricular ejection fraction (LVEF): HFrEF – LVEF < 40%, HFmrEF – LVEF 40-49 %, HFpEF – LVEF ≥ 50%. A total of 2 677 patients with available echocardiography were enrolled. Subsets of HFrEF, HFmrEF and HFpEF consisted of 1 169 (43.7%), 720 (26.9%) and 788 (29.4%) patients, respectively.

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klinických znakov, mechanickej a elektrickej remodelácie. Najvýraznejší rozdiel v týchto charakteristikách bol medzi HFrEF a HFpEF. Pacienti s HFrEF boli najviac symptomatickí, s najvyššou prevalenciou symptómov kongescie, tried NYHA III/IV a znakov SZ. Najmenej symptomatickí, s najnižšou mierou kongescie a znakov SZ boli pacienti s HFpEF. Demografia, symptomatológia a klinické znaky HFmrEF boli intermediárne medzi HFrEF a HFpEF. Menej výrazné rozdiely medzi jednotlivými fenotypmi SZ sme zistili pri komorbiditách a diagnostike.

Záver: Fenotypy HFrEF, HFmrEF a HFpEF sa významne epidemiologicky odlišujú. HFmrEF je intermediárny typ SZ, bez univerzálnej podobnosti HFrEF alebo HFpEF. Prieskum EPIT-HF prezentuje prvú epidemiologickú charakteristiku všetkých troch fenotypov SZ na Slovensku. Tab. 6, Lit. 15, online full text (Free, PDF) www.sks.sk

Kľúčové slová: chronické srdcové zlyhávanie – srdcové zlyhávanie s redukovanou ejekčnou frakciou – srdcové zlyhávanie s mid-range ejekčnou frakciou – srdcové zlyhávanie so zachovanou ejekčnou frakciou – epidemiológia

Results: We found significant differences between three phenotypes of HF in terms of demography, etiology, symptomatology, clinical signs and mechanical and electrical remodeling. The most striking differences in these characteristics were observed between HFrEF and HFpEF. Patients with HFrEF were most symptomatic, with the highest prevalence of congestive symptoms, NYHA class III/IV and with significantly highest prevalence of HF signs. The least symptomatic, with the lowest rate of congestive symptoms and HF signs, were patients with HFpEF. Demography, symptomatology and clinical signs in HFmrEF were intermediate between HFrEF and HFpEF. Less significant differences between the HF phenotypes were found for co-morbidities and diagnostics.

Conclusion: The phenotypes of HFrEF, HFmrEF and HFpEF are epidemiologically significantly different. HFmrEF is an intermediate type of HF without universal similarity to HFrEF or HFpEF. The EPIT-HF survey presents the first epidemiological characteristics of all three phenotypes of HF in Slovakia. Tab. 6, Ref. 15, online full text (Free, PDF) www.sks.sk

Key words: chronic heart failure – heart failure with reduced ejection fraction – heart failure with mid-range ejection fraction – heart failure with preserved ejection fraction – epidemiology

Európska kardiologická spoločnosť (ESC) zmenila od roku 2016 klasifikáciu chronického srdcového zlyhávania (SZ). Podľa ejekčnej frakcie ľavej komory (EFĽK) sa rozlišujú tri fenotypy: SZ s redukovanou ejekčnou frakciou (HFrEF, heart failure with reduced ejection fraction), SZ s mid-range ejekčnou frakciou (HFmrEF, heart failure with mid-range ejection fraction) a SZ so zachovanou ejekčnou frakciou (HFpEF, heart failure with preserved ejection fraction) (1).

Podľa ESC majú HFrEF a HFpEF odlišný epidemiologický a etiologický profil. Charakteristiky HFmrEF sú „medzi nimi" (1). Podľa American College of Cardiology a American Heart Association sa javia charakteristiky, liečba a prognóza pacientov s EFĽK 41 – 49 % podobné pacientom s HFpEF (2).

Existuje však len malý počet prác, ktoré hodnotili epidemiológiu všetkých troch typov SZ. Je to dané dvoma dôvodmi. Prvým je krátky čas od etablovania HFmrEF. Druhým je skutočnosť, že registre SZ a komunitné štúdie systematicky vylučovali pacientov s HFmrEF alebo ich častejšie zahŕňali do HFpEF (3). V európskom (a mediteránskom) regióne poskytuje najrozsiahlejšiu databázu informácií ESC HF Long-Term register (5 460 pacientov) (3). Najrozsiahlejší súbor vôbec predstavuje americký register OPTIMIZE-HF u 20 118 hospitalizovaných pacientov (4). Epidemiológiu troch fenotypov SZ podľa definície ESC hodnotila aj japonská štúdia CHART-2 (5) a európska štúdia TIME-CHF (6).

Údaje o epidemiológii chronického SZ na Slovensku sú značne limitované (7), pričom o HFmrEF neboli doposiaľ

The European Society of Cardiology (ESC) has changed the classification of chronic heart failure (HF) since 2016. According to the left ventricular ejection fraction (LVEF), three phenotypes of HF are distinguished: heart failure with reduced ejection fraction (HFrEF), heart failure with mid-range ejection fraction (HFmrEF) and heart failure with preserved ejection fraction (HFpEF) (1).

HFrEF and HFpEF have a different epidemiologic and etiologic profile. The characteristics of HFmrEF are "in between them" (1). According to American College of Cardiology and American Heart Association, the characteristics, treatment and prognosis of patients with HF and LVEF 41-49% are similar to patients with HFpEF (2).

However, there is only a small number of publications that have evaluated the epidemiology of all three types of HF. This is due to two reasons.The first is the short time since HFmrEF has been established.The second is that HF registers and community studies systematically excluded patients with HFmrEF or more often they included them in HFpEF (3). In European (and Mediterranean) region, the most extensive databasis of epidemiologic information is provided by the ESC HF Long-Term registry (5 460 patients) (3). The absolutely most extensive cohort is presented by the US OPTIMIZE-HF registry (20 118 hospitalized patients) (4). The epidemiology of all three phenotypes of HF as defined by the ESC was also evaluated in the Japanese study CHART-2 (5) and in the European study TIME-CHF (6).

Data on the epidemiology of chronic HF in Slovakia are very limited (7), while the data on chronic HFmrEF have

publikované žiadne údaje. Preto prezentujeme prieskum EPIT-HF (**Epi**demiology and **T**herapy for **H**eart **F**ailure), zameraný na epidemiológiu troch fenotypov chronického SZ u ambulantných pacientov.

Pacienti a metodika

EPIT-HF je neintervenčná observačná prospektívna multicentrická štúdia. Prieskum realizovalo 161 lekárov, z toho 115 kardiológov (71,4 %) a 46 internistov (28,6 %). Každý lekár mal prospektívne zaradiť 20 následných ambulantných pacientov s diagnózou chronického SZ, stanovenou podľa odporúčaní ESC, platných v čase realizácie štúdie (8). Do prieskumu boli zaradení pacienti vo veku ≥ 18 rokov. Neexistovali žiadne exklúzne kritériá na zaradenie pacientov, vrátane doterajšej liečby. Echokardiografické údaje sa získavali z posledného dostupného vyšetrenia pred zaradením do prieskumu, vrátane dňa zaradenia. Prieskum sa vykonával dotazníkovou formou. Lekári získavali údaje počas jediného vyšetrenia. Nábor sa realizoval v októbri a novembri 2015.

Do prieskumu EPIT-HF zaradili lekári spolu 3 280 pacientov. Z nich boli echokardiografické údaje dostupné u 2 677 pacientov (81,6 %). Títo pacienti predstavovali súbor prezentovanej práce. V prieskume sme porovnali epidemiologické charakteristiky HFrEF, HFmrEF a HFpEF. Fenotypy SZ boli definované v zmysle aktuálnych odporúčaní ESC podľa hodnoty EFĽK: HFrEF – EFĽK < 40 %, HFmrEF – EFĽK 40 – 49 %, HFpEF – EFĽK ≥ 50 % (1). Analyzovali sme základnú demografiu, etiológiu SZ, symptomatológiu, klinické znaky SZ, komorbidity a diagnostiku SZ. V práci neuvádzame údaje o liečbe SZ, pretože je predmetom samostatnej práce v tomto časopise.

Štatistická analýza

Kategorické dáta sú vyjadrené relatívnymi početnosťami. Spojité premenné vyjadrujeme ako priemer ± smerodajná odchýlka. Frekvenciu výskytu kategorických dát medzi podsúbormi sme porovnali Pearsonovým χ^2 testom nezávislosti, respektíve Fisherovým presným testom. Na porovnanie stredných hodnôt spojitých premenných medzi podsúbormi sme použili analýzu rozptylu (ANOVA). V prípade, že výsledok ANOVA bol štatisticky významný, ďalej sme použitím metódy LSD zisťovali, medzi ktorými podsúbormi bol výsledok štatisticky významný. Ako hranicu štatistickej významnosti sme zvolili hodnotu $p < 0,05$. Všetky kalkulácie sa realizovali pomocou SPSS Statistics 20.0 software (IBM Corp. Released 2011. IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY: IBM Corp.).

not yet been published. Therefore, we present the EPIT-HF (**Epi**demiology and **T**herapy for **H**eart **F**ailure) survey, focused on the epidemiology of three phenotypes of chronic HF in outpatients.

Patients and methods

EPIT-HF is a non-interventional, observational, prospective, multicentric study. The survey was performed by 161 physicians, including 115 cardiologists (71.4%) and 46 internists (28.6%). Each physician had to include prospectively 20 consecutive outpatients diagnosed with chronic HF according to the ESC guidelines valid at the time of the realization of this study (8). The survey included patients aged at least 18 years. There were no exclusion criteria for patient enrollment, including previous treatment. Echocardiographic data were obtained from the last available examination including the date of the study inclusion. The survey was conducted by questionnaire form. The physicians obtained the data during a single examination. Recruitment took place in October and November 2015.

A total of 3 280 patients were enrolled in the EPIT-HF survey. Of these, echocardiographic data were available in 2 677 patients (81.6%). These patients represented a study group of the presented publication. In this survey, we compared epidemiologic characteristics of HFrEF, HFmrEF and HFpEF. The HF phenotypes were defined by the current guidelines of ESC according to LVEF value: HFrEF – LVEF < 40%, HFmrEF – LVEF 40-49 %, HFpEF – LVEF ≥ 50% (1). We analyzed demography, etiology, symptomatology, clinical signs of HF, comorbidities and diagnostics of HF. In this publication we do not provide data on HF therapy because it is the subject of a separate study in this journal.

Statistical analysis

Categorial values are expressed as percentages, and continuous variables are expressed as mean ± standard deviation. We compared the occurrence of categorial data between the subsets by the Pearson´s χ^2 test of independence or Fisher´s exact test. The differences between mean values of continuous variables were compared using analysis of variance (ANOVA). If the ANOVA result was statistically significant, we subsequently determined, using the LSD method, among which subsets the result was statistically significant. Differences were declared to be statistically significant at $p < 0.05$. All statistical calculations were carried out using SPSS Statistics 20.0 software (IBM Corp. Released 2011. IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY: IBM Corp.).

Výsledky

Do podsúborov HFrEF, HFmrEF a HFpEF bolo zaradených 1 169 (43,7%), 720 (26,9 %), respektíve 788 (29,4 %) pacientov.

V **tabuľke 1** je demografia a etiológia SZ. Významné rozdiely medzi jednotlivými typmi SZ sme pozorovali pri komparácii takmer všetkých charakteristík. Najvýznamnejšie sa odlišovali HFrEF a HFpEF (vo všetkých položkách).

Symptomatológia SZ je uvedená v **tabuľke 2**. Pre všetky symptómy uniformne klesala ich prevalencia od najvyššej pri HFrEF cez intermediárnu pri HFmrEF k najnižšej pri HFpEF. Najviac symptomatickí boli pacienti s HFrEF, najmenej symptomatickí pacienti s HFpEF. Tomu zodpovedá aj významne najvyšší podiel štádií NYHA III + IV pri HFrEF. Najvýraznejší rozdiel symptomatológie sme pozorovali medzi HFrEF a HFpEF.

V **tabuľke 3** sú nálezy a objektívne znaky SZ. Rovnako ako pri symptomatológii aj prevalencia všetkých znakov SZ

Results

Subsets of HFrEF, HFmrEF and HFpEF consisted of 1 169 (43.7%), 720 (26.9%) and 788 (29.4%) patients, respectively.

Demography and etiology are presented in **Table 1**. Significant differences between the individual HF phenotypes were observed when comparing almost all characteristics. Most notably HFrEF and HFpEF were different (in all items).

Symptomatology of the HF is presented in **Table 2**. For all symptoms, their prevalence uniformly decreased from highest in HFrEF, through intermediate in HFmrEF, to lowest in HFpEF. The most symptomatic were patients with HFrEF, the least symptomatic were patients with HFpEF. This corresponds to the significantly highest proportion of NYHA III + IV classes in HFrEF. The most striking difference in symptomatology was observed between HFrEF and HFpEF.

The objective findings and signs of HF are in **Table 3**. As well as symptomatology, the prevalence of all HF signs

Table 1 Demography and causes of heart failure
Tabuľka 1 *Demografia a príčiny srdcového zlyhávania*

	Heart failure *(Srdcové zlyhávanie)*			**P**			
	HFrEF (n=1 169)	HFmrEF (n=720)	HFpEF (n=788)	Overall	1 vs 2	1 vs 3	2 vs 3
Demography *(Demografia)*							
Age (years)	66.2±10.9	68.2±10,2	69.2±9.5	**<0.001**	**<0.001**	**<0.001**	0.066
Female gender	31.3%	40.1%	49.9%	**<0.001**	**<0.001**	**<0.001**	**<0.001**
Primary cause of heart failure *(Primárna príčina srdcového zlyhávania)*							
CAD	60.4%	64.3%	35.8%	**<0.001**	0.097	**<0.001**	**<0.001**
Hypertension	6.9%	15.6%	39.0%	**<0.001**	**<0.001**	**<0.001**	**<0.001**
D-CMP	25.9%	8.2%	3.1%	**<0.001**	**<0.001**	**<0.001**	**<0.001**
Valvular disease	5.7%	10.0%	15.9%	**<0.001**	**<0.001**	**<0.001**	**<0.001**
Other causes	0.9%	1.8%	6.4%	**<0.001**	0.137	**<0.001**	**<0.001**

HFrEF – heart failure with reduced ejection fraction *(srdcové zlyhávanie s redukovanou ejekčnou frakciou;* 1) HFmrEF – heart failure with mid-range ejection fraction *(srdcové zlyhávanie s mid-range ejekčnou frakciou;* 2) HFpEF – heart failure with preserved ejection fraction *(srdcové zlyhávanie so zachovanou ejekčnou frakciou;* 3) CAD – coronary artery disease *(koronárna artériová choroba)*, D-CMP – dilated cardiomyopathy *(dilatačná kardiomyopatia)*. Overall *(celkovo),* age (years) *vek (roky)*, hypertension *(hypertenzia),* valvular diseases *(chlopňové chyby)*, other causes *(iné príčiny)*. Continuous variables are expressed as mean ± standard deviation *(spojité premenné sú vyjadrené ako priemer ± smerodajná odchýlka)*.

Table 2 Symptoms of heart failure
Tabuľka 2 *Symptómy srdcového zlyhávania*

	Heart failure *(Srdcové zlyhávanie)*			**P**			
	HFrEF (n=1169)	HFmrEF (n=720)	HFpEF (n=788)	Overall	1 vs 2	1 vs 3	2 vs 3
Dyspnoea	71.6%	68.6%	64.2%	**0.003**	0.177	**<0.001**	0.072
Orthopnoea	8.6%	4.9%	2.8%	**<0.001**	**0.002**	**<0.001**	**0.042**
Peripheral oedema	32.1%	28.5%	24.9%	**0.003**	0.101	**<0.001**	0.116
Weakness/fatigue	52.5%	49.4%	43.5%	**<0.001**	0.201	**<0.001**	**0.023**
NYHA class I+II	48.3%	61.8%	72.8%	**<0.001**	**<0.001**	**<0.001**	**<0.001**
NYHA class ≥ III	51.7%	38.2%	27.2%	**<0.001**	**<0.001**	**<0.001**	**<0.001**

Legend as in Table 1*(legenda ako v tabuľke 1)*. Dyspnoea – *dýchavica*, orthopnoea – *ortopnoe*, peripheral oedema – *periférne edémy*, weakness/fatigue – *slabosť/únava*, class – *trieda*.

Table 3 Signs of the heart failure
Tabuľka 3 *Znaky srdcového zlyhávania*

	Heart failure *(Srdcové zlyhávanie)*			**P**			
	HFrEF (n=1 169)	HFmrEF (n=720)	HFpEF (n=788)	Overall	1 vs 2	1 vs 3	2 vs 3
SBP (mmHg)	128.2±17.8	135.1±17.4	133.7±16.6	**<0.001**	**<0.001**	**<0.001**	0.108
DBP (mmHg)	77.5±10.4	79.9±10.4	79.0±10.1	**<0.001**	**<0.001**	**0.002**	0.074
Heart rate (bpm)	73.5±13.0	74.5±14.9	71.7±12.6	**<0.001**	0.115	**0.003**	**<0.001**
BMI	28.7±5.0	29.7±4.9	29.8±4.9	**<0.001**	**<0.001**	**<0.001**	0.835
Clinical signs of heart failure *(Znaky srdcového zlyhávania)*							
Rales	31.6%	23.1%	16.0%	**<0.001**	**<0.001**	**<0.001**	**<0.001**
Oedema	36.4%	31.9%	27.4%	**<0.001**	**0.047**	**<0.001**	0.055
Fluidothorax	8.3%	5.0%	4.1%	**<0.001**	**0.007**	**<0.001**	0.388
3rd heart sound	10.8%	6.1%	2.4%	**<0.001**	**<0.001**	**<0.001**	**<0.001**
Hepatomegaly	14.2%	8.6%	7.4%	**<0.001**	**<0.001**	**<0.001**	0.392
Ascites	4.2%	0.6%	1.1%	**<0.001**	**<0.001**	**<0.001**	0.271
Cachexia	5.0%	3.6%	2.2%	**0.006**	0.206	**<0.001**	0.121

Legend as in Table 1 *(legenda ako v tabuľke 1)*. SBP – systolic blood pressure *(systolický tlak krvi)*, DBP – diastolic blood pressure *(diastolický tlak krvi)*, BMI – body mass index *(index telesnej hmotnosti).* Heart rate (bpm) *(srdcová frekvencia, údery/min)*, rales *(chrôpky),* oedema *(opuchy)*, 3rd heart sound *(3. srdcová ozva),* hepatomegaly *(hepatomegália),* cachexia *(kachexia)*

zhodne klesala od HFrEF cez HFmrEF k HFpEF. Najvyššia miera kongescie aj kachexie bola u pacientov s HFrEF, najnižšia u pacientov s HFpEF. Pri porovnaní klinických znakov pri troch fenotypoch SZ bol najzjavnejší rozdiel medzi HFrEF a HFpEF, rovnako ako pri etiológii a symptomatológii SZ.

Významné kardiálne a extrakardiálne komorbidity pri SZ sú v **tabuľke 4**. Na rozdiel od symptomatológie a znakov SZ sme pri komorbiditách nezistili žiadny uniformný „vzorec" minimálnej, respektíve maximálnej prevalencie pri niektorom konkrétnom fenotype SZ. Rovnako na rozdiel od predchádzajúcich dvoch tabuliek nemožno konštatovať najvýraznejší rozdiel prevalencie komorbidít medzi niektorými dvoma fenotypmi SZ. Zaujímavé je, že pre viaceré kardiovaskulárne komorbidity (všetky typy cievnych mozgových príhod, fibrilácia predsiení, periférne artériové okluzívne ochorenie dolných končatín) a extravaskulárne komorbidity (chronické ochorenie obličiek KDIGO ≥ 3. št., anémie, aktívne malignity) sme nezistili žiadny prevalenčný rozdiel medzi fenotypmi SZ.

V **tabuľke 5** je prehľad diagnostických metód pri SZ. Echokardiografia v tabuľke uvedená nie je, pretože ju malo 100 % pacientov pri všetkých typoch SZ. Logickou podmienkou pre klasifikáciu pacientov bola totiž stanovená hodnota EFĽK. Mieru využitia echokardiografie v praxi vieme stanoviť v neselektovanom základnom súbore všetkých pacientov, zaradených do EPIT-HF. Absolvovalo ju 2 677 z 3 280 pacientov (81,6 %). Podobne ako pri komorbiditách sme nezistili všeobecnú minimálnu alebo maximálnu prevalenciu diagnostických modalít pri niektorom fenotype SZ. Na rozdiel od symptomatológie a znakov nemožno konštatovať ani žiadny univerzálny rozdiel v prevalencii diagnostických metód medzi fenotypmi.

also consistently decreased from HFrEF through HFmrEF to HFpEF. The highest rate of both congestion and cachexia was in patients with HFrEF, the lowest in patients with HFpEF. When comparing the clinical signs in all HF phenotypes, the most obvious difference was found between HFrEF and HFpEF, as well as in the etiology and symptomatology of HF.

Important cardiac and extracardiac comorbidities are shown in **Table 4**. Unlike symptomatology and HF signs, we did not find any uniform "formula" of minimal or maximal prevalence of comorbidities in some specific HF phenotype. Likewise, unlike the previous three tables, the most pronounced difference in the prevalence of comorbidities between some HF phenotypes could not be ascertained. Interestingly, we have not found different prevalence of several cardiovascular comorbidities (all types of stroke, atrial fibrillation, peripheral arterial occlusive disease) and several extravascular comorbidities (chronic kidney disease KDIGO at least stage 3, anemia, active malignancies) between the HF phenotypes.

The overview of diagnostic methods in HF is in **Table 5**. Echocardiography is not included, because it was performed in 100% of patients in all types of HF. Namely, the LVEF value was required for the determination of HF phenotype. The rate of use of echocardiography in practice can be determined in a non-selected group of all patients enrolled in EPIT-HF. It was performed in 2 677 of 3 280 patients (81.6%). As with comorbidities, we have not observed the generally minimal or maximum prevalence of diagnostic modalities in some HF phenotype. In contrast to symptomatology and signs, there was no universal difference in the prevalence of diagnostic methods between the phenotypes.

Table 4 Comorbidities of the heart failure
Tabuľka 4 *Komorbidity srdcového zlyhávania*

	Heart failure *(Srdcové zlyhávanie)*			**P**			
	HFrEF (n=1169)	HFmrEF (n=720)	HFpEF (n=788)	Overall	1 vs 2	1 vs 3	2 vs 3
Myocardial infarction	54.1%	50.6%	29.1%	**<0.001**	0.142	**<0.001**	**<0.001**
PCI	42.2%	39.9%	25.6%	**<0.001**	0.336	**<0.001**	**<0.001**
CABG	16.7%	18.6%	10.2%	**<0.001**	0.289	**<0.001**	**<0.001**
Arterial hypertension	85.0%	92.6%	93.7%	**<0.001**	**<0.001**	**<0.001**	0.475
AFib/AFlu	38.2%	41.3%	38.8%	0.396	0.191	0.776	0.344
Dyslipidemia	82.0%	85.8%	88.2%	**<0.001**	**0.030**	**<0.001**	0.192
Stroke	14.8%	14.6%	13.7%	0.475	0.898	0.499	0.625
– ischemic	13.9%	14.0%	12.7%	0.694	0.946	0.499	0.449
– intraparench. hem.	0.8%	0.4%	0.8%	0.617	0.553	1.0	0.511
– SAH	0.2%	0.1%	0.3%	0.863	1.0	1.0	1.0
TIA	12.4%	14.3%	14.5%	0.328	0.234	0.197	0.942
Carotid revasc.	4.9%	3.6%	1.7%	**<0.001**	0.205	**<0.001**	**0.022**
– catheter-based	2.4%	1.5%	0.6%	**0.011**	0.244	**0.004**	0.130
– surgical	2.1%	1.4%	0.9%	0.083	0.293	**0.044**	0.466
PAOD lower extr.	20.0%	18.9%	18.5%	0.682	0.591	0.449	0.895
Revasc. lower extr.	4.4%	3.9%	3.9%	0.843	0.638	0.730	1.0
– catheter-based	2.6%	2.4%	2.5%	0.960	0.880	1.0	0.869
– surgical	1.5%	1.5%	1.4%	0.964	1.0	0.851	0.834
Diabetes mellitus	42.5%	49.3%	43.9%	**0.005**	**0.004**	0.541	**0.036**
– type I	0.3%	1.7%	0.8%	**0.008**	**0.003**	0.215	0.153
– type II	42.2%	47.6%	43.2%	0.058	**0.022**	0.675	0.087
CKD*	18.7%	19.9%	18.8%	0.811	**0.548**	1.0	0.602
COPD	14.7%	18.6%	17.0%	0.075	**0.029**	0.183	0.419
Bronchial asthma	6.9%	9.3%	9.5%	0.069	0.065	**0.041**	0.930
Thyroid dysfunction	9.4%	13.2%	14.0%	**0.002**	0.102	**0.002**	0.665
– hypothyreosis	8.1%	11.5%	11.8%	**0.010**	**0.015**	**0.008**	0.873
– hyperthyreosis	1.3%	1.7%	2.2%	0.328	0.551	0.148	0.575
Anemia	21.4%	19.6%	20.8%	0.642	0.381	0.778	0.564
Malignancy	5.7%	10.6%	8.0%	**0.001**	**<0.001**	**0.049**	0.086
– active	1.5%	2.8%	2.0%	0.133	0.059	0.372	0.400
– in remission	4.3%	7.8%	6.0%	0.006	0.002	0.111	0.184

Legend as in Table 1 *(legenda ako v tabuľke 1)*. PCI – percutaneous coronary intervention *(perkutánna koronárna intervencia)*, CABG – coronary artery bypass grafting *(aorto-koronárny by-pass)*, AFib – atrial fibrillation *(fibrilácia predsiení)*, AFlu – atrial flutter *(flutter predsiení)*, intraparench. hem.– intraparenchymal hemorrhage *(parenchýmová hemorágia)*, SAH – subarachnoidal hemorrhage *(subarachnoidálna hemorágia)*, TIA – transient ischemic attack *(tranzitórny ischemický atak)*, revasc. – revascularization *(revaskularizácia)*, PAOD – peripheral arterial occlusive disease *(periférne artériové okluzívne ochorenie)*, extr. – extremities *(končatiny)*, CKD – chronic kidney disease *(chronické ochorenie obličiek)*, * – glomerular filtration rate *(glomerulová filtrácia)* < 60 mL/min/1.73 m^2, COPD – chronic obstructive pulmonary disease *(chronická obštrukčná choroba pľúc).* Myocardial infarction *(infarkt myokardu),* arterial hypertension *(artériová hypertenzia),* stroke *(mozgová príhoda),* ischemic *(ischemická),* carotid *(karotická),* catheter-based *(katétrová),* surgical *(chirurgická),* lower *(dolné),* bronchial asthma *(astma bronchiale),* thyroid dysfunction *(dysfunkcia štítnej žľazy),* malignancy *(malignita),* active *(aktívna),* in remission *(v remisii)*

V **tabuľke 6** sú základné EKG a echokardiografické parametre. Pri HFrEF bola signifikantne najvyššia prevalencia blokády ľavého ramienka a najdlhšie trvanie komplexu QRS. Všetky fenotypy SZ sa významne navzájom odlišovali vo všetkých hodnotených echokardiografických parametroch. Pacienti s HFrEF mali najväčší priemer ľavej komory a ľavej predsiene a stupeň mitrálnej regurgitácie. Najlepšie parametre mali pacienti s HFpEF.

Basic ECG and echocardiographic parameters are in **Table 6**. In patients with HFrEF the significantly highest prevalence of left bundle branch block was found and the longest QRS complex duration. Three HF phenotypes significantly differed from each other in all evaluated echocardiographic parameters. Patients with HFrEF had the largest left ventricular and left atrial diameter and mitral regurgitation degree. Relatively the best parameters were found in patients with HFpEF.

Table 5 Diagnostics of heart failure
Tabuľka 5 *Diagnostika srdcového zlyhávania*

	Heart failure *(Srdcové zlyhávanie)*			**P**			
	HFrEF (n=1 169)	HFmrEF (n=720)	HFpEF (n=788)	Overall	1 vs 2	1 vs 3	2 vs 3
ECG	99.7%	99.7%	99.6%	0.941	1.0	1.0	1.0
Chest X-ray	78.5%	77.4%	81.7%	0.089	0.567	0.085	**0.040**
Natriur. peptides	59.9%	48.6%	49.0%	**<0.001**	**<0.001**	**<0.001**	0.885
– NT-proBNP	57.0%	45.8%	47.2%	**<0.001**	**<0.001**	**<0.001**	0.606
– BNP	2.9%	2.8%	1.8%	0.264	1.0	0.136	0.225
Thyroid profile	57.6%	55.8%	66.5%	**<0.001**	0.473	**<0.001**	**<0.001**
Iron profile*	31.6%	29.6%	33.3%	0.310	0.383	0.460	0.134
Stress test	26.4%	25.3%	37.2%	**<0.001**	0.590	**<0.001**	**<0.001**
– ergometric	24.6%	22.8%	34.3%	**<0.001**	0.405	**<0.001**	**<0.001**
– stress ECHO	0.4%	0.6%	1.1%	0.150	0.738	0.098	0.271
– stress scintigr.	1.2%	1.3%	1.5%	0.814	1.0	0.551	0.668
Coronarography	67.0%	58.6%	45.4%	**<0.001**	**<0.001**	**<0.001**	**<0.001**
– invasive	64.2%	55.1%	41.0%	**<0.001**	**<0.001**	**<0.001**	**<0.001**
– CT angiography	2.3%	3.2%	4.6%	0.021	0.242	**0.009**	0.185
CT scan**	3.1%	3.8%	5.0%	0.105	0.432	**0.041**	0.313
MR scan	2.1%	1.7%	3.7%	**0.022**	0.607	**0.033**	**0.017**

Legend as in Table 1 *(legenda ako v tabuľke 1)*. Natriur. – natriuretic *(nátriuretický)*, * – including ferritin and transferrin saturation *(vrátane ferritínu a saturácie transferínu)*, ECHO – echocardiography *(echokardiografia)*, scintigr. – scintigraphy *(scintigrafia)*, ** – other indications than CT coronary angiography *(iné indikácie ako koronárna CT angiografia),* Chest X-ray (*RTG hrudníka),* natriur. peptides *(natriuretické peptidy)*, thyroid profile *(profil štítnej žlazy),* iron profile *(profil železa),* stress test *(záťažový test),* ergometric *(ergometrický),* stress *(záťažový),* stress scintigr. *(záťažová scintigrafia),* coronarography *(koronarografia)*, invasive *(invazívna),* angiography *(angiografia)*

Table 6 ECG and echocardiography
Tabuľka 6 *EKG a echokardiografia*

	Heart failure *(Srdcové zlyhávanie)*			**P**			
	HFrEF (n=1 169)	HFmrEF (n=720)	HFpEF (n=788)	Overall	1 vs 2	1 vs 3	2 vs 3
ECG *(EKG)*							
Atrial fibrillation	23.7%	26.5%	22.1%	0.124	0.170	0.412	**0.047**
LBBB	24.2%	13.9%	11.6%	**<0.001**	**<0.001**	**<0.001**	0.188
QRS (ms)	109.1±28.3	104.7±34.2	104.7±40.8	**0.004**	**0.007**	**0.005**	0.997
Echocardiography *(echokardiografia)*							
LVEF	31.9±5.2%	42.2±2.8%	55.3±5.5%	**<0.001**	**<0.001**	**<0.001**	**<0.001**
LVEDD (mm)	60.5±8.3	56.7±6.2	53.2±6.7	**<0.001**	**<0.001**	**<0.001**	**<0.001**
LAD (mm)	47.6±6.5	46.7±6.5	44.9±6.5	**<0.001**	**0.002**	**<0.001**	**<0.001**
MR (degree)	1.7±0.8	1.4±0.9	1.2±0.9	**<0.001**	**<0.001**	**<0.001**	**<0.001**

Legend as in Table 1 *(legenda ako v tabuľke 1)*. LBBB – left bundle branch block *(blokáda ľavého ramienka)*, LVEF – left ventricular ejection fraction *(ejekčná frakcia ľavej komory)*, LVEDD – left ventricular enddiastolic diameter in parasternal long axis view *(enddiastolický priemer ľavej komory v parasternálnej dlhej osi)*, LAD – left atrial diameter in parasternal long axis view *(priemer ľavej predsiene v parasternálnej dlhej osi)*, MR – mitral regurgitation *(mitrálna regurgitácia)*, Atrial fibrillation *(fibrilácia predsiení)*

Diskusia

Prieskum EPIT-HF predstavuje prvý súbor epidemiologických údajov o všetkých troch fenotypoch SZ na Slovensku podľa aktuálnej definície ESC (1).

V našom súbore bol podiel pacientov s HFrEF 43,7 %, HFmrEF 26,9 % a HFpEF 29,4 %. Podiel je čiastočne odlišný od registrov ESC HF LT a OPTIMIZE-HF. V aktuálnom registri ESC HF Long-Term (5 460 ambulantných pacientov)

Discussion

The EPIT-HF survey is the first epidemiologic study in all three phenotypes of HF according to the current ESC definition (1) in Slovakia.

In our study group, the proportion of patients with HFrEF, HFmrEF and HFpEF was 43.7%, 26.9% and 29.4%, respectively. These rates are somewhat different from the ESC HF Long-Term and OPTIMIZE-HF registries. In the current ESC HF

bola percentuálna početnosť fenotypov SZ 58,6 %, 23,8 % a 17,6 % (3). V staršom americkom registri OPTIMIZE-HF (20 118 hospitalizovaných pacientov) bola početnosť 53,6 %, 19,5 % a 26,9 % (4). Okrem nich existujú ešte dve práce, hodnotiace epidemiológiu troch fenotypov SZ podľa definície ESC – japonská štúdia CHART-2 (3 480 pacientov; 61,9 %, 17,1 %, respektíve 21,0 %) (5) a európska štúdia TIME-CHF (622 pacientov; 64,6 %, 17,4 %, respektíve 18,0 %) (6). Starší izraelský národný prieskum HFSIS z roku 2007 zahrnul 2 842 hospitalizovaných pacientov so SZ a známou EFĽK (9). Podľa post-hoc analýzy v zmysle aktuálnej klasifikácie SZ išlo o 52,0 % pacientov s HFrEF, 21,1 % pacientov s HFmrEF a 26,9 % pacientov s HFpEF.

Percentuálny podiel fenotypov ovplyvňuje viacero faktorov. U ambulantných pacientov so SZ dominuje HFrEF, kým u hospitalizovaných pacientov sa popisuje bimodálna distribúcia s porovnateľným podielom HFrEF a HFpEF a nízkym podielom HFmrEF (3). V súboroch zo špecializovaných kardiologických pracovísk jednoznačne dominuje HFrEF, kým v súboroch z interných a geriatrických pracovísk je podstatne vyšší podiel HFpEF (3). V štúdiách, ktoré neboli dizajnované na komparáciu fenotypov SZ, sa podiel pacientov s HFpEF uvádza 40 – 72 %, pričom v ostatných rokoch narastá (10 – 13). Do tohto podielu však boli obvykle zahrnutí aj pacienti s EFĽK 41 – 49 %. Tým si vysvetľujeme, že v EPIT-HF bol podiel pacientov s HFpEF nižší, 29 %.

Demografia

Všetky dostupné registre sa jednotne zhodujú, že vek významne narastá v poradí HFrEF – HFmrEF – HFpEF. Identicky vo všetkých registroch podiel žien plynulo narastal v rovnakom poradí, od 22 – 38 % pri HFrEF po 39 – 68 % pri HFpEF (3 – 6). Vo všetkých prácach sa zistil štatisticky významný rozdiel veku a pohlavia medzi ľubovoľnými dvoma fenotypmi SZ. Naše výsledky sú úplne zhodné. Možno konštatovať, že všetky tri fenotypy SZ sa navzájom významne odlišujú podľa veku a pohlavia. Pacienti s HFrEF sú relatívne mladší, s nižším podielom žien. Naopak, pacienti s HFpEF sú významne starší a s významne vyšším podielom žien.

Etiológia

Koronárna artériová choroba (KACh) sa uvádza ako príčina systolickej dysfunkcie ĽK u 39 – 54 % pacientov (14). KACh bola vo väčšine prác a aj v EPIT-HF dominantnou (nadpolovičnou) etiológiou HFrEF a HFmrEF, pričom prevalencia tejto príčiny bola pri oboch fenotypoch porovnateľná (15). Etiologický podiel KACh bol pri HFpEF vždy významne nižší ako pri ostatných dvoch typoch SZ (4 – 6). Prekvapivou výnimkou je európsky register ESC HF-LT, kde pri všetkých typoch SZ bola najčastejšou príčinou hypertenzia (3). Vysvetlením je pravdepodobne skutočnosť, že len v tomto

Long-Term Registry (5 460 outpatients), the percentage of HF phenotypes was 58.6%, 23.8% and 17.6%, respectively (3). In the older US OPTIMIZE-HF registry (20 118 hospitalized patients), the percentage was 53.6%, 19.5% and 26.9%, respectively (4). In addition, there are two further papers evaluating the epidemiology of all three HF phenotypes according to the ESC definition – the Japanese CHART-2 study (3 480 patients, 61.9%, 17.1% and 21.0%, respectively) (5) and the European TIME-CHF study (622 patients, 64.6%, 17.4% and 18.0%, respectively) (6). The older Israeli national HFSIS survey published in 2007 included 2 842 hospitalized patients with HF and known LVEF (9). As to the post-hoc analysis, according to the current HF classification, there were 52.0% of patients with HFrEF, 21.1% of patients with HFmrEF and 26.9% of patients with HFpEF.

The percentage of HF phenotypes is influenced by several factors. In outpatients HFrEF dominates, while in hospitalized patients a bimodal distribution is described with a comparable proportion of HFrEF and HFpEF and low proportion of HFmrEF (3). HFrEF clearly dominates in the cohorts from the specialized cardiologic departments, while in the cohorts from internal and geriatric departments a significantly higher proportion of HFpEF was presented (3). In studies that were not designed to compare HF phenotypes, the proportion of patients with HFpEF is stated to be 40-72%, with a continuous increase in recent years (10-13). However, the patients with LVEF 41-49% were usually included in the cohorts with HFpEF. This explains the lower proportion of the patients with HFpEF in EPIT-HF (29%).

Demography

All available registries consistently agree that age significantly increases in the order of HFrEF – HFmrEF – HFpEF. Equally, in all registries, the proportion of women grew steadily in the same order, from 22-38% in HFrEF to 39-68% in HFpEF (3-6). In all studies, a statistically significant age and gender difference was found between any two HF phenotypes. Our results are exactly the same. It can be stated that all three HF phenotypes differ significantly from each other by age and gender. Patients with HFrEF are relatively younger, with a lower proportion of women. Conversely, patients with HFpEF are significantly older, with a significantly higher proportion of women. Patients with HFmrEF are intermediate in terms of age and gender.

Etiology

Coronary artery disease (CAD) is reported to be the cause of left ventricular (LV) systolic dysfunction in 39-54% of patients (14). CAD was the dominant etiology (more than 50% of cases) of HFrEF and HFmrEF in majority of the studies as well as in EPIT-HF survey. The prevalence of this cause was comparable in both phenotypes (15). The etiological proportion of CAD was always significantly lower for HFpEF than for the other two types of HF (4-6). A surprising exception is the European ESC HF Long-Term registry, where arterial

registri sa mohlo uviesť viacero príčin SZ, kým v ostatných prácach len jediná príčina.

Etiologický význam artériovej hypertenzie (AHT) je vzhľadom na KACh úplne inverzný. V registroch a aj v EPIT-HF podiel AHT ako príčiny SZ stúpal v poradí HFrEF (7 – 20 %) – HFmrEF (16 – 28 %) – HFpEF (31 – 57 %) (4 – 6). Etiologický význam AHT sa pri HFmrEF viac blížil k HFrEF ako k HFpEF (rovnako ako pri KACh).

Očakávaným faktom je, že vo všetkých registroch a aj v našom súbore významne klesal etiologický podiel D-KMP v poradí HFrEF (20 – 35 %) – HFmrEF (8 – 28 %) – HFpEF (1 – 12 %). Relatívne novou informáciou je plynulý nárast príčinného podielu chlopňových chýb v poradí HFrEF (3 – 6 %) – HFmrEF (6 – 10 %) – HFpEF (11 – 16 %) (3, 5, 6).

Stanovenie etiológie SZ môže byť v niektorých prípadoch vzhľadom na prekrývanie diagnóz problematické. Sumárne možno konštatovať, že etiológia SZ sa pri jednotlivých fenotypoch vzájomne významne odlišuje. HFmrEF sa vzhľadom na príčinnosť viac približuje HFrEF ako HFpEF.

Symptomatológia

V registri EPIT-HF bola najvyššia prevalencia všetkých symptómov kongescie aj slabosti/únavy pri HFrEF, pričom bola signifikantne vyššia ako pri HFpEF. Symptomatológia HFmrEF bola analogická ako pri HFrEF. Z literatúry je k dispozícii na porovnanie len menšia štúdia Rickenbachera a spol. s opačným zistením (6). V ich súbore bola tendencia k najvýraznejšej symptomatológii pri HFpEF. Zrejme to súvisí so skutočnosťou, že kým v EPIT-HF bolo len 27 % pacientov s HFpEF v triede NYHA III + IV, v citovanej práci až 82 %.

Najvyšší podiel najviac symptomatických pacientov v triedach NYHA III a IV sme zistili pri HFrEF, najnižší pri HFpEF. Aj v registri ESC HF-LT a v štúdii CHART-2 bola najvyššia prevalencia tried NYHA III + IV u pacientov s HFrEF (3, 5).

Klinické znaky

Hodnoty STK vo všetkých prácach a aj v našom súbore jednotne významne stúpali v poradí HFrEF – HFmrEF – HFpEF. Pri DTK boli medzi fenotypmi len minimálne rozdiely. Ani pri srdcovej frekvencii neboli absolútne rozdiely medzi typmi SZ výrazné, 0 – 5 úderov/min (3 – 6). Zistili sme, že priemerná hodnota SF 73,5/min u našich pacientov s HFrEF je vyššia ako odporúčaná hodnota do 70/min. Preto je potrebná intenzívnejšia bradykardizujúca liečba betablokátormi a/alebo ivabradínom.

Všeobecne sa traduje, že pacienti s HFpEF sú obéznejší ako pacienti s HFrEF. Niektoré registre však tento predpoklad nepotvrdili (3, 5). V štúdii TIME-CHF (6) a v EPIT-HF bol síce najvyšší priemerný BMI pri HFpEF a najnižší pri HFrEF, ale rozdiel nebol výrazný, 1 – 2 indexové body.

hypertension (AHT) was reported to be the most common cause for all types of HF (3). An explanation is probably the fact that only in this registry several causes of HF could be given, whereas in other studies only one cause of HF was required.

The etiological significance of AHT is completely inverse to CAD. In the registries as well as in the EPIT-HF, the causal share of AHT increased in the order HFrEF (7-20%) – HFmrEF (16-28%) – HFpEF (31-57%) (4-6). The etiological significance of AHT in HFmrEF was closer to HFrEF than to HFpEF (equally as in CAD).

The expected fact is that the etiological proportion of dilated cardiomyopathy decreased significantly in all registries as well as in our survey in the order HFrEF (20-35%) – HFmrEF (8-28%) – HFpEF (1-12%). We have confirmed a continuous increase in the causal fraction of valvular diseases in the order HFrEF (3-6%) – HFmrEF (6-10%) – HFpEF (11-16%) (3, 5, 6).

Determination of the HF etiology may be problematic in some cases due to overlapping of diagnoses. In summary it can be concluded that the etiology of HF differs significantly in individual phenotypes. In terms of causal relationship HFmrEF is more likely to approach HFrEF than HFpEF.

Symptomatology

In EPIT-HF, the highest prevalence of all congestive symptoms, weakness and fatigue was in HFrEF, whereas it was significantly higher than in HFpEF. The symptomatology of HFmrEF was analogous to HFrEF. In the literature, only a small study by Rickenbacher et al. is available for comparison, with an opposite finding (6). In their study group, there was a tendency for the most pronounced symptomatology in HFpEF. Obviously this correlates with the fact that while in EPIT-HF there were only 27% of patients with HFpEF in the NYHA classes III and IV, they were up to 82% in the cited study.

We found the highest proportion of the most symptomatic patients in NYHA classes III and IV in HFrEF, the lowest in HFpEF. Also in the ESC HF-Long-Term registry and in the CHART-2 study, the highest prevalence of NYHA classes III and IV was in patients with HFrEF (3, 5).

Clinical signs

Systolic blood pressure increased uniformly and significantly in all publications and even in our study group in the order HFrEF – HFmrEF – HFpEF. In diastolic blood pressure, there were only minimal differences between the phenotypes. Even with the heart rate, absolute differences between HF phenotypes were not considerable, 0-5 bpm (3-6). We found that the mean heart rate of 73.5 bpm in our patients with HFrEF is higher than the recommended value up to 70 bpm. Therefore, more intensive heart rate lowering treatment with beta-blockers and/or ivabradine is required.

In general, there is an awareness that HFpEF patients are more obese than patients with HFrEF. However, some registries did not confirm this premise (3, 5). In the TIME-

V súbore EPIT-HF sme zistili, že prevalencia všetkých znakov centrálnej aj periférnej kongescie a aj kachexia významne klesajú v poradí HFrEF – HFmrEF – HFpEF. Žiadna iná práca však našu skúsenosť nepotvrdila. Práve naopak, v registroch ESC HF-LT, OPTIMIZE-HF a v štúdii TIME-CHF bola najvyššia miera kongescie pri HFpEF (3, 4, 6). Tento rozpor nemožno vysvetliť jednoducho len rôznou mierou preskripcie diuretík, pretože vo všetkých citovaných prácach a aj v EPIT-HF bola vždy vyššia pri HFrEF ako pri HFpEF. Uvedené práce a EPIT-HF mali podobnú demografiu a etiológiu SZ. Rozpor bude iste multifaktoriálny, ale jasné vysvetlenie nie je k dispozícii.

Komorbidity

Komorbidity významne ovplyvňujú prognózu pacientov so SZ. Podľa tradičnej predstavy je ich význam najdominantnejší u pacientov s HFpEF.

Prevalencia prekonaného infarktu myokardu a koronárnych revaskularizačných výkonov (CABG, PKI) je podľa literatúry a našich výsledkov prakticky identická pri HFrEF a HFmrEF a je zásadne nižšia pri HFpEF (3, 5, 6). Zaujímavé je, že ischémia myokardu sa vo vzťahu k SZ správa podobne pri HFmrEF ako pri HFrEF.

Artériová hypertenzia a hypercholesterolémia sú jednoznačne najčastejšie komorbidity pri SZ. Prevalencia artériovej hypertenzie je relatívne najnižšia pri HFrEF (66 – 85 %). Významne vyššia (a takmer identická) je pri HFmrEF a HFpEF (74 – 94 %) (3 – 6). Je zrejmé, že hypertenzia sa vo vzťahu k SZ správa inak ako ischémia myokardu (pozri aj vyššie časť „Etiológia“).

Jediný zásadný rozdiel medzi literatúrou a EPIT-HF z oblasti komorbidít sa týka fibrilácie predsiení. Všetky práce sa zhodujú v tom, že jej prevalencia významne narastá v poradí HFrEF – HFmrEF – HFpEF (3 – 6). Dominantným vysvetlením je najmä analogický vzostup prevalencie artériovej hypertenzie. Prekvapením je takmer identická prevalencia fibrilácie/flutteru predsiení v EPIT-HF pri všetkých typoch SZ (38 – 41 %). Čiastočne sa na tom môže podieľať skutočnosť, že rozptyl prevalencie hypertenzie v EPIT-HF bol medzi fenotypmi nižší ako v literatúre. Predpokladáme tiež, že s porovnateľnou prevalenciou súvisí fakt, že priemerná veľkosť ľavej predsiene nebola v našom súbore zásadne odlišná medzi fenotypmi SZ (45 – 48 mm).

Diabetes mellitus je podľa literatúry a výsledkov EPIT-HF porovnateľne častou komorbiditou pri všetkých troch fenotypoch SZ, nezdá sa byť „viazaný“ na žiadny z nich (3 – 6). Na Slovensku sa javí byť asociácia diabetu a SZ výraznejším problémom ako vo svete (prevalencia diabetu pri SZ 43 – 49 % vs 31 – 40 %).

Pre ložiskovú ischémiu myokardu, chronickú obštrukčnú chorobu pľúc a chronické ochorenie obličiek (CKD) platí analogické tvrdenie ako pre diabetes. Ich prevalencia v registroch, štúdiách a aj v EPIT-HF sa zásadne neodlišuje medzi

CHF study (6) and also in EPIT-HF, the highest mean BMI was in HFpEF and the lowest in HFrEF but the difference was not considerable, 1-2 index points.

In EPIT-HF, we found that the prevalence of all signs of central and peripheral congestion and cachexia significantly decreased in the order HFrEF – HFmrEF – HFpEF. No other study has confirmed our experience. On the contrary, in the ESC HF Long-Term and OPTIMIZE-HF registries and in the TIME-CHF study, the congestion rate was the highest in patients with HFpEF (3, 4, 6). This discrepancy cannot be explained simply by a different rate of diuretics prescription, because in all of the cited papers and in EPIT-HF it was higher in HFrEF than in HFpEF. The above-mentioned papers and EPIT-HF had a similar demography and etiology of the HF. The contradiction will certainly be multifactorial, but an obvious explanation is not available.

Comorbidities

Comorbidities significantly influence the prognosis of HF patients. According to the traditional concept, their importance is most dominant in HFpEF.

The prevalence of preceding myocardial infarction and coronary revascularization (CABG, PCI) is virtually identical for HFrEF and HFmrEF, and is substantially lower for HFpEF, according to the literature and our results (3, 5, 6). Interestingly, the relation of myocardial ischemia to HF is similar in HFmrEF as in HFrEF.

Arterial hypertension and hypercholesterolemia are clearly the most common comorbidities in HF. The prevalence of arterial hypertension is relatively lowest in HFrEF (66-85%). It is significantly higher (and almost identical) in HFmrEF and HFpEF (74-94%) (3-6). It is obvious that hypertension behaves in relation to HF otherwise than myocardial ischemia (see also the section “Etiology” above).

The only fundamental difference between the literature and EPIT-HF regarding comorbidities concerns atrial fibrillation. All papers agree that its prevalence significantly increases in the order HFrEF – HFmrEF – HFpEF (3-6). The predominant explanation is, in particular, an analogical increase in the prevalence of AHT. Surprisingly, the prevalence of atrial fibrillation/atrial flutter in EPIT-HF was almost identical in all types of HF (38-41%). This is partly due to the fact that the variance of AHT prevalence among the phenotypes in EPIT-HF was lower than in the literature. We also assume that the comparable prevalence is related to the fact that the mean left atrial diameter was not significantly different in our study group among the HF phenotypes (45-48 mm).

Diabetes mellitus, according to the literature and EPIT-HF results, is comparatively common in all three HF phenotypes, and does not appear to be dominantly “bound” to some of them (3-6). In Slovakia, the association of diabetes and HF appears to be a more prominent problem than in the world (diabetes prevalence in HF 43-49% vs. 31-40%) (3-6).

fenotypmi SZ (3 – 6). Stanovisko k CKD je však limitované pre odlišnú definíciu v rôznych prácach.

V literatúre jestvuje len málo údajov o paralelnom porovnaní výskytu anémie pri všetkých fenotypoch SZ (6). V našom súbore bola anémia pomerne častá, ale jej prevalencia bola takmer identická pri všetkých typoch SZ (20 – 21 %).

Malignity sú podľa literatúry komorbiditou SZ u 12 – 17 % pacientov, bez podstatného rozdielu medzi fenotypmi SZ (5, 6). V týchto prácach sa však nešpecifikuje, či ide o aktívne nádory a/alebo malignity v remisii. V EPIT-HF bol výskyt aktívnych malignít pri troch typoch SZ porovnateľný (2 – 3 %). Malignity v remisii boli komorbiditou u 4 – 8 % pacientov, najmenej pri HFrEF.

Diagnostika

V prieskume EPIT-HF sme podľa základných EKG a echokardiografických parametrov zistili, že tri fenotypy SZ sa navzájom odlišujú v zmysle elektrickej a anatomickej remodelácie. Najmarkantnejší rozdiel je medzi HFrEF a HFpEF, pričom HFmrEF predstavuje medzistupeň.

Podľa TIME-CHF a EPIT-HF je komplex QRS najširší pri HFrEF a signifikantne najužší pri HFpEF (6). Podľa registra ESC HF-LT (3) a našich výsledkov prevalencia blokády ľavého ramienka významne klesá v poradí HFrEF (24 %) – HFmrEF (14 – 15 %) – HFpEF (9 – 12 %).

Typický remodelačný obraz ĽK je excentrická hypertrofia ĽK pri HFrEF a koncentrická remodelácia alebo koncentrická hypertrofia pri HFpEF, v menšej miere aj pri HFmrEF (6, 10, 11). Tomu zodpovedá jednotný pokles priemernej hodnoty rozmeru ĽK v parasternálnej dlhej osi vo všetkých štúdiách aj v našej práci, so signifikantným rozdielom medzi ľubovoľnými fenotypmi: HFrEF (61 – 65 mm) – HFmrEF (52 – 58 mm) – HFpEF (48 – 53 mm) (3, 5, 6). Potvrdili sme údaj z registra ESC HF-LT (3), že aj prevalencia významnej mitrálnej regurgitácie je signifikantne odlišná medzi hocakými dvoma fenotypmi SZ, pričom klesá v poradí ako pri priemere ĽK.

Rozdiel v remodelácii ľavej predsiene je podstatne menej zjavný ako pri ľavej komore. Priemer ľavej predsiene sa v našom súbore síce významne medzi fenotypmi odlišoval, ale absolútne hodnoty rozdielu boli malé (do 3 mm). Analogické výsledky uvádza literatúra. V štúdii TIME-CHF bol dokonca rozmer ľavej predsiene identický pri všetkých typoch SZ (6) a v registri ESC HF-LT bol jej objem takmer rovnaký pri HFrEF a HFpEF (3).

Echokardiografia je najzákladnejšia diagnostická metóda pri SZ. Existuje predstava, že jej dostupnosť na Slovensku je bezproblémová. V prieskume EPIT-HF sa však vykonala len u 81,6 % z 3 280 pacientov so SZ. Môže to súvisieť so skutočnosťou, že 28,6 % participujúcich lekárov boli internisti, pre ktorých môže byť metodika horšie dostupná ako pre kardiológov. Na porovnanie v staršom izraelskom prieskume

For myocardial ischemia, chronic obstructive pulmonary disease and chronic kidney disease (CKD), an analogous claim to that for diabetes applies. Their prevalence in registries, studies, and EPIT-HF basically does not differ between HF phenotypes (3-6). However, the opinion on CKD is limited due to a different definition in various publications.

In the literature, there is only limited data on the parallel comparison of the prevalence of anemia in all HF phenotypes (6). In our set, anemia was quite common, and its prevalence was almost identical in all HF types (20-21%).

According to the literature, malignancies are a comorbidity in 12-17% of patients with HF, with no significant difference between HF phenotypes (5, 6). However, these papers do not specify whether they evaluated only active tumors or even malignancies in remission. In EPIT-HF, the prevalence of active malignant tumors in all three HF types was comparable (2-3%). We found the malignancies in remission as comorbidity in 4-8% of patients, the least in HFrEF.

Diagnostics

In the EPIT-HF survey, according to basic ECG and echocardiographic parameters, we found that the three HF phenotypes differ significantly from each other in terms of electrical and anatomical remodeling. The most striking difference was between HFrEF and HFpEF, with HFmrEF being an intermediate phenotype.

According to TIME-CHF and EPIT-HF, the QRS complex is the broadest in HFrEF and significantly narrowest in HFpEF (6). According to ESC HF Long-Term registry (3) and our results, the prevalence of left bundle branch block significantly decreases in the order HFrEF (24%) – HFmrEF (14-15%) – HFpEF (9-12%).

A typical pattern of LV remodeling is eccentric hypertrophy in HFrEF and concentric remodeling or concentric hypertrophy in HFpEF, to a lesser extent also in HFmrEF (6, 10, 11). This corresponds to a uniform decrease in the mean LV diameter in the parasternal long axis in all studies and in our survey, with a significant difference between any phenotypes: HFrEF (61-65 mm) – HFmrEF (52-58 mm) – HFpEF (48-53 mm) (3, 5, 6). We have confirmed the ESC HF Long-Term data (3) that the prevalence of significant mitral regurgitation is significantly different among all HF phenotypes, decreasing in the same order as LV diameter.

The difference in left atrial remodeling is considerably less apparent than in the left ventricular remodeling. Left atrial diameter differed significantly between the phenotypes in EPIT-HF but the absolute difference was small (up to 3 mm). Analogous results are reported in the literature. In the TIME-CHF study, even left atrial diameter was identical for all HF types (6) and in the ESC HF Long-Term registry its volume was almost the same in HFrEF and HFpEF (3).

Echocardiography is the most fundamental diagnostic method in HF. In general, there is an awareness that it is available in Slovakia without problems. However, echocardiography

HFSIS malo echokardiografiu len 69,3 % z 4 102 pacientov, hospitalizovaných pre SZ (9).

Záťažové testy sa realizovali u 25 – 37 % našich pacientov, viac pri HFpEF ako pri HFrEF. Vysvetlením je predpoklad, že mnohí pacienti s HFrEF priamo absolvujú koronarografiu bez záťažového testu (najmä kvôli infarktu myokardu). Absolútne dominuje ergometria. Postavenie zobrazovacích záťažových modalít je u nás marginálne. Prevalencia koronárnej angiografie významne klesala v EPIT-HF od HFrEF (67 %) k HFpEF (45 %), pričom jednoznačne dominuje invazívna koronarografia. Koronárna CT angiografia (CTCA) sa stále používa len okrajovo (2 – 5 % pacientov). Rovnako CT srdca (z inej indikácie ako CTCA) a MR srdca sú u pacientov so SZ zriedkavé (3 – 5 %, respektíve 2 – 4 %). Súvisí to pravdepodobne s faktom, že „iné" príčiny SZ (mimo KACh, hypertenzie, dilatačnej kardiomyopatie a chlopňových chýb) boli výnimočné (1 – 6 %) **(tabuľka 1)**. Z literatúry nám nie je známa štúdia, porovnávajúca diagnostické modality pri všetkých fenotypoch SZ.

Limitácie

Pacientov sme klasikovali do fenotypov SZ podľa EFĽK. Hodnotenie EFĽK môže predstavovať bias, pretože: 1. nepodliehalo centrálnej validácii, 2. meranie EFĽK nebolo štandardizované, 3. akceptovala sa posledná dostupná hodnota EFĽK. Naša echokardiografická klasifikácia SZ zodpovedala dizajnu „real world data". Kategóriu HFmrEF sme vytvorili až v post-hoc analýze, pretože v čase realizácie prieskumu ešte neexistovala. Diagnóza SZ nebola centrálne validovaná. Všetky epidemiologické údaje môžu byť čiastočne ovplyvnené tranzíciou medzi fenotypmi SZ. Kategorizácia pacienta do fenotypu SZ podľa posledného dostupného echokardiografického vyšetrenia nemusela byť totožná s kategorizáciou v deň zaradenia do prieskumu (EFĽK sa mohla u časti pacientov od uvedeného vyšetrenia významne zmeniť).

Závery

V prieskume EPIT-HF sme prezentovali prvý súbor epidemiologických údajov o všetkých troch fenotypoch SZ na Slovensku. Zistili sme, že HFrEF, HFmrEF a HFpEF predstavujú vzájomne odlišné fenotypy SZ v zmysle demografie, etiológie, symptomatológie, klinických znakov SZ, mechanickej a elektrickej remodelácie. Najvýraznejší rozdiel vo všetkých uvedených charakteristikách bol medzi HFrEF a HFpEF. Klinické charakteristiky HFmrEF sú intermediárne medzi HFpEF a HFrEF. Najviac symptomatickí sú pacienti s HFrEF, ktorí majú najvyššiu mieru kongescie aj kachexie.

was performed in the EPIT-HF survey in only 81.6% of the 3 280 patients with HF. This may be related to the fact that 28.6% of participating physicians were internists for whom it may be less available than for cardiologists. By comparison, in the older Israeli HFSIS survey, echocardiography was performed in only 69.3% of 4 102 patients hospitalized for HF (9).

Stress tests were performed in 25-37% of our patients, significantly more frequently in HFpEF than in HFrEF. This can be explained by the fact that many patients with HFrEF directly undergo coronarography without a stress test (mainly due to myocardial infarction). Ergometric exercise absolutely dominated among the stress tests. The importance of the imaging stress modalities is marginal in Slovakia.

The prevalence of coronary angiography significantly decreased in EPITF-HF from HFrEF (67%) to HFpEF (45%). Invasive coronarography clearly dominated. Coronary CT angiography (CTCA) is still used only marginally (2-5% of patients). Likewise, cardiac CT scans (other indications than CTCA) and cardiac MR scans are rarely performed in patients with HF (3-5% and 2-4%, respectively). This is probably related to the fact that "other" causes of HF (except CAD, AHT, dilated cardiomyopathy and valvular diseases) were exceptional (1-6%, **Table 1**). To our best knowledge there is no available paper in the literature comparing diagnostic modalities in all HF phenotypes.

Limitations

The patients were classified into the HF phenotypes according to LVEF. Evaluation of the LVEF may present a bias because: 1. it was not subjected to central validation, 2. LVEF measurement was not standardized, 3. the last available LVEF was accepted. Our echocardiographic HF classification corresponded to the design of "real world data". We created the HFmrEF category only in the post-hoc analysis because it did not exist at the time of the survey. Diagnosis of the HF has not been centrally validated. All epidemiological data may be partially influenced by the transition between the HF phenotypes. The classification of the patient into the HF phenotype according to the latest available echocardiographic examination did not have to be the same as the classification on the day of the survey (LVEF may have changed significantly in some patients since the last examination).

Conclusion

In the EPIT-HF survey, we present the first set of epidemiological data on all three phenotypes of chronic HF in Slovakia. We found that HFrEF, HFmrEF and HFpEF represent mutually different phenotypes of HF in terms of demography, etiology, symptomatology, clinical signs of HF, and mechanical and electrical remodeling. The most significant difference in all of these characteristics was between HFrEF and HFpEF. The clinical characteristics of HFmrEF are intermediate be-

Najmenšia prevalencia symptómov s najnižšou mierou kongescie je pri HFpEF.

Autori

Obaja autori sa signifikantne podieľali na štúdii. JD naplánoval štúdiu a vytvoril jej dizajn, zodpovedal za zber dát a napísal rukopis. RŠ vykonal štatistickú analýzu a revidoval predložený rukopis.

Poďakovanie

Ďakujeme všetkým 161 participujúcim lekárom za podporu projektu EPIT-HF a aktívnu účasť na zbere údajov.

Konflikt záujmov

Autori deklarujú, že neexistuje žiadny konflikt záujmov vo vzťahu k tejto práci.

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tween HFpEF and HFrEF. The most symptomatic are patients with HFrEF who have the highest degree of congestion and cachexia. The lowest prevalence of symptoms with the lowest degree of congestion was found in HFpEF.

Contributors

All authors have contributed substantially the body of work. JD planned and designed the study, carried out data collection and wrote the manuscript. RS undertook the statistical analysis and revised the manuscript for submission.

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Conflict of interest

None declared.

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