Hemodynamic profile changes in reaction to nitroglycerin in patients with heart failure with mildly reduced ejection fraction: A pilot study

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INTRODUCTION

There are 3 types of heart failure (HF) — with reduced (HFrEF; ≤40%), mildly reduced (HFmrEF; 41%–49%), and preserved (HFpEF; ≥50%) left ventricular ejection fraction (LVEF) [1]. The HFmrEF type is the least known. Like the HFrEF group, the HFmrEF type is characterized by a higher prevalence of younger, male individuals with a history of coronary artery disease. On the other hand, ambulatory HFmrEF patients have lower mortality (more like HFpEF).

This study aimed to assess the hemodynamic profile of patients with HFmrEF at rest and after sublingual administration of 0.4 mg of nitroglycerin (NTG) in comparison to those with HFrEF and HFpEF using noninvasive electrical cardiometry (EC).

EC is based on thoracic bio-impedance changes during the cardiac cycle [2]. Notwithstanding its limitations, EC is a useful tool in the management of patients with HF [3, 4]. Vein and artery dilatation after NTG administration leads to preload and afterload reduction and consequently to a stroke volume (SV) and cardiac output (CO) increase [5].

METHODS

The study was performed in clinically stable subjects (with a history of HF as well as HF diagnosed *de novo)* on the last day of hospitalization for acute decompensated heart failure (ADHF), defined as an exacerbation of typical HF signs/symptoms, requiring the administration of iv. diuretics (at least 40 mg of furosemide or its equivalent). The control groups for HFmrEF patients were those with HFpEF and HFrEF. There was no control group of healthy subjects. The clinical profile of patients was assessed by the data from medical interviews and records, laboratory test results, and measured echocardiographic parameters while the noninvasive hemodynamic profile, at rest and after the NTG administration, was assessed by EC using the ICON® (OSYPKA Medical) device. The most important exclusion criteria were age <18 years; ADHF caused by: acute coronary syndrome, significant valvular disease, tachyarrhythmia; percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG) during the current hospitalization; severe dyspnea or orthopnea; chronic lung diseases; stage 5 chronic kidney disease or on dialysis; contraindications for NTG administration (including BP <90/60 mm Hg); implantable cardiac devices with a "rate response" mode (contraindication for EC); the ICON® report quality index below 90% (to avoid potential bias in readings obtained from patients with atrial fibrillation or overweight).

After approximately 60 cardiac cycles (stable readings on the device), the first EC report was generated (at rest) and the second — 2–3 minutes after NTG administration. Each report (automatically generated by the ICON®) contains the mean values (from the last 60 heart cycles) of each measured hemodynamic parameter. A control blood pressure measurement was performed only in the case of a reported adverse event.

The χ^2, χ^2 with Yates' correction, and Fisher's exact tests were carried out to compare categorical variables, depending on the number of counts. The difference in continuous variables was calculated with the Mann-Whitney U test (when 2 groups were compared) or the Kruskal-Wallis test (in the case of >2 groups). The

majority of variables did not follow normal distributions (as verified with the Shapiro-Wilk test). Therefore, all numerical variables are presented as median and interquartile range, and nonparametric tests were used for all calculations (as they presented a comparable statistical power to their parametric equivalents in the case of the normally distributed variables).

The study was approved by the Ethics Committee at the Medical University of Łódz (RNN/108/19/KE).

RESULTS AND DISCUSSION

Overall, 45 patients (hospitalized between January 1 and June 30, 2021), were enrolled in this pilot study, including 15 consecutive patients from each HF type, and most of them were men (n = 32; 71%). The full clinical study group characteristics and their hemodynamic profile changes are presented in Supplementary material, *Tables S1* and *S2*. Diabetes was significantly more frequent in the HFpEF group. The HFrEF group had a higher left ventricular end-diastolic dimension (P <0.001) and lower right ventricular systolic function (tricuspid annular plane systolic excursion [TAPSE]; P = 0.003). All patients were receiving β-blockers (except for nebivolol or carvedilol), mineralocorticoid receptor antagonists, angiotensin-converting-enzyme inhibitors (ACEI; 86.7%) or angiotensin II receptor antagonists (ARB, 13.3%), and loop diuretics (only furosemide or torsemide). The study was completed before the latest HF guidelines release and none of the patients was receiving angiotensin receptor-neprilysin inhibitor (ARNI) or sodium-glucose co-transporter-2 inhibitors (SGLT2i).

The results of the hemodynamic profile at rest showed a lower systolic time ratio (STR; P = 0.02) and pre-ejection period (PEP; P = 0.049) in the HFmrEF group in comparison to the HFrEF group.

After NTG administration, in patients with HFmrEF, in comparison to HFrEF, we observed a decline in the median of stroke volume and stroke volume index (SV/SI; P = 0.01/0.02), cardiac output and cardiac index (CO/CI; P = 0.01/0.01), cardiac performance index (CPI; P = 0.049), and corrected flow time (FTC; P = 0.04), and an increase in systemic vascular resistance and its indexed values (SVR/SVRI; P = 0.03/0.03).

The median of change in the following parameters: SV, SI, CO, CI, FTC, SVR, SVRI, and CPI after NTG administration in the HFmrEF group had an opposite direction in comparison to the patients with HFrEF (P <0.05) (Figure 1, Supplementary material, *Table S2*). This effect was observed in some patients in all study groups, however, most frequently in the HFmrEF group (number of patients with the opposite NTG reaction – HFrEF, n = 2; HFpEF, n = 3; HFmrEF, n = 6) — all three groups were compared with Fisher's exact test (performed on a 3×2 table), and no difference was observed (P = 0.19). Unfortunately, none of the analyzed clinical parameters showed an association with a particular type of NTG reaction (Supplementary material, *Table S1*).

To the best of our knowledge, this is the first study to evaluate hemodynamic profile changes in HFmrEF patients in comparison to those with HFpEF and HFrEF.

Our study confirms the intermediate character of HFmrEF patients' clinical profile, which is widely described in the literature [6–9]. The hemodynamic profile of all three groups shared the same characteristics at rest with significant differences exclusively in STR and PEP between HFmrEF and HFrEF patients. Unfortunately, there is no data in the current literature referring to this observation, especially SVR which can be measured only by the ICON® device.

The analysis of the hemodynamic profile after NTG administration brings the most intriguing results. Firstly, we found significant differences between HFmrEF and HFrEF in 8 parameters, including the main hemodynamic parameters associated with blood flow: SV/SI, CO/CI, and SVR/SVRI. Moreover, the median change in the same parameters in the HFmrEF group (SV, SI, CO, CI, FTC, SVR, SVRI, and CPI) had an opposite direction. In the case of the HFpEF and HFrEF patients CO and SV were increasing, while they were decreasing in HFmrEF. In the case of SVR/SVRI, the decline in the HFrEF and HFpEF patients was accompanied by an icrease in those with HFmrEF. The opposite reaction to NTG (CO and SV decline and SVR increase) was observed in some patients in all study groups; however, most frequently in the HFmrEF group, and a higher incidence of this phenomenon caused the opposite direction of the median change of each parameter.

In the randomized clinical trial with NO-donor — BMS-986231 (HFrEF patients only), the authors observed a slight but statistically significant decline in SV and SVI [10]. In one study, the invasive SV and CO measurements in 257 patients with HF showed that HFrEF patients had a greater increase in SV and CO in comparison to HFpEF [11], caused by more frequent opposite NTG reaction in HFpEF (HFpEF: 35% vs HFrEF: 9%; P <0.0001). The reaction was caused by the increased end-diastolic pressure of left ventricle (LV) (preload). Again, patients with HFmrEF were not included, as a mean (SD) EF was 22% (9%) and 63% (6%) (P <0.0001), so the frequency of the opposite NTG reaction in HFmrEF remains unknown. Our study suggests that the incidence of this phenomenon is the highest in the HFmrEF group and may be caused by the combination of both systolic and diastolic dysfunction of LV (confirmed in all HFmrEF subjects by echocardiography).

The most important limitation of the study is a small group of patients and lack of a control group of healthy subjects. Further studies on a greater population are required to confirm our observations.

In conclusion, HFmrEF differs significantly from HFrEF in terms of changes of the hemodynamic profile after NTG administration, considering EC parameters of the blood flow (SV, SI, CO, CI, SVR, SVRI) and heart muscle contractility (CPI, FTC). The median change of all the above-mentioned parameters showed the opposite direction after NTG

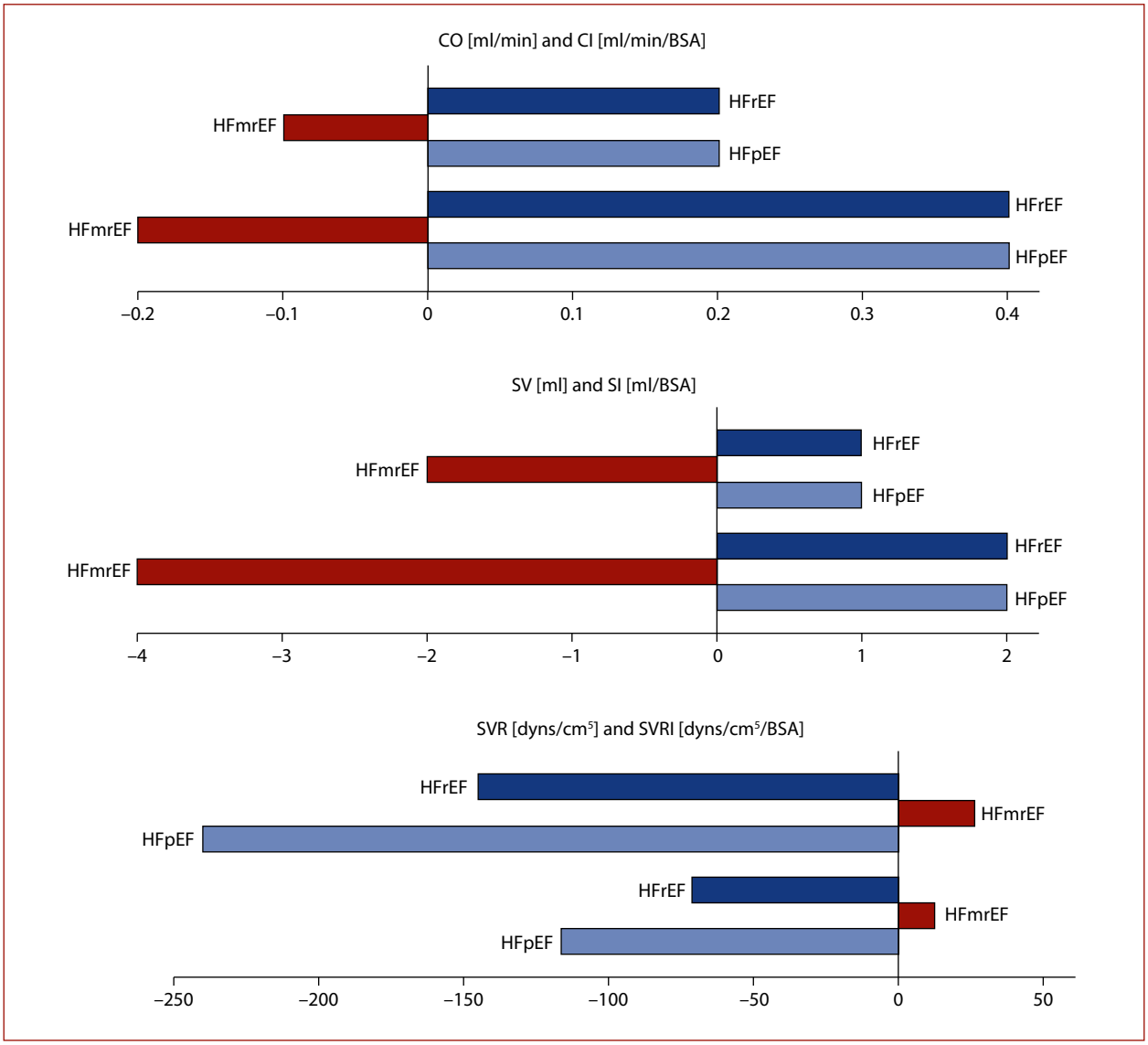

Figure 1. Median change in basic hemodynamic parameters after nitroglycerin administration (HFmrEF vs. HFpEF: P = NS; HFmrEF vs. HFrEF; P <0.05)

Abbreviations: BSA, body surface area; CI, cardiac index; CO, cardiac output; dyn, force unit in the CGS metric system; HFmrEF, heart failure with mildly reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; SI, stroke volume index; SV, stroke volume; SVR, systemic vascular resistance; SVRI, systemic vascular resistance index

administration in the HFmrEF group in comparison to the HFpEF and HFrEF groups. The opposite reaction to NTG occurred most frequently in the HFmrEF group.

Supplementary material

Supplementary material is available at https://journals.viamedica.pl/kardiologia_polska

Article information

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