Původní sdělení | Original research article

Relationship between Functional Capacity and Medication Adherence in Heart Failure

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SOUHRN

Úvod: Studie se zabývala vztahem mezi subjektivní klasifikací New York Heart Association (NYHA) a objektivní zátěžovou kapacitou (měřenou pomocí vrcholového příjmu kyslíku [VO_{2peak}]) u pacientů se srdečním selháním a dále tím, zda je tento vztah ovlivněn adherencí k medikaci.
Metody: Byly analyzovány údaje 170 pacientů se srdečním selháním z registru Level-CHF. Adherence byla hodnocena pomocí testování koncentrace léků v séru. Objektivní zátěžová kapacita byla hodnocena pomocí spiroergometrie na bicyklovém ergometru.
Výsledky: Hodnota objektivní maximální spotřeby kyslíku často převyšovala odpovídající subjektivní třídu NYHA se 46% shodou, rozdíly se projevovaly zejména na krajních koncích spektra. Byly zaznamenány drobné odchylky v subjektivním hodnocení třídy NYHA v souvislosti s adherencí k medikaci, ale nebyly pozorovány žádné podstatné rozdíly.
Závěr: Výsledek upozorňuje na rozdíly mezi subjektivním a objektivním hodnocením funkční kapacity u pacientů se srdečním selháním. To by mělo vést k většímu využívání objektivních měření při klinickém rozhodování na základě funkční kapacity a k využívání přímo měřených hodnot VO_{2peak} nad subjektivní třídou NYHA. Dodržování medikace významně nezměnilo subjektivně-objektivní trendy NYHA.

Keywords:
Adherence
Cardiopulmonary exercise testing
Chronic heart failure
Drug therapy
Serum drug levels

ABSTRACT

Introduction: This study investigated the relationship between the subjective New York Heart Association (NYHA) class and objective exercise capacity (VO_{2peak}) in patients with heart failure and whether it is influenced by medication adherence.
Methods: Data from 170 heart failure patients in the Level-CHF register were analysed, and adherence was assessed by serum drug level testing. Objective exercise capacity was assessed by cardiopulmonary exercise testing using a bicycle ergometer.
Results: Objective VO_{2peak} frequently exceeded the subjective NYHA class with 46% concordance, especially at the extreme ends of the spectrum. Minor differences in subjective NYHA class in relation to medication adherence were noted, but no substantial disparity was observed.
Conclusion: These findings highlight the discrepancies between subjective and objective assessments of functional capacity in patients with heart failure. This calls for a greater use of objective measurements in clinical decision-making based on functional capacity and for preference of direct VO_{2peak} values over subjective NYHA categories. Medication adherence did not significantly alter the subjective-objective NYHA trends.

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Introduction

Chronic heart failure (CHF) is one of the greatest challenges facing contemporary medicine.[1] As the prognosis of patients with acute cardiovascular diseases improves, the number of patients who experience heart failure increases. The five-year mortality rate of patients with chronic heart failure is as high as 67%.[2] In the United States, the total cost of heart failure treatment is projected to increase from $21 billion to $53 billion between 2012 and 2030.[3]

The New York Heart Association (NYHA) classification is used almost exclusively to assess the subjective functional capacity in patients with heart failure.[4] NYHA class is part of virtually every outpatient check-up. It is used in a wide range of decisions with a significant impact on the patient's future management and prognosis (e.g., escalation of heart failure treatment, indication for cardiac resynchronization therapy [CRT], mechanical cardiac support [MCS], or heart transplantation).[5]

The advantage is that NYHA class correlates well with patient prognosis and is simple to use.[6] The problem with NYHA class is that it is a subjective classification based on the patient's description of symptoms, which may be biased due to both patient simulation and dissimulation. In a comparison between two specialist cardiologists, the assessment of the patient's NYHA was the same in only 54% of cases.[7]

A 6-minute walk test and cardiopulmonary exercise test is used to determine the patient's objective functional capacity. The parameter being measured is the maximum oxygen utilization by the tissues (VO_{2max}) or the highest achievable oxygen utilization during the test (VO_{2peak}). This variable correlates well with patient's prognosis.[8] VO_{2max} is used by the objective Weber classification. According to Weber, the patients were divided into classes A–D.[9] The verbal assessment of the patient's symptoms is corresponding to these classes, which is similar to the individual NYHA classes (Table 1). There is no 100% consensus on the conversion between subjective and objective functional capacity. Usually, the conversion shown in Table 1 is used in practice. Conversion via metabolic equivalents (MET) can be used to compare NYHA class grades to objective VO_{2max}, as shown in Table 1.[9–11]

In a clinical practice, physicians often ascertain the level of medication adherence using only patient self-report, which is an indirect method of adherence detection and may be subject to a significant bias.[12] Only a fraction of patients answers truthfully, and the question is whether the same patients giving false (intentionally or unintentionally) information about their medication use gives similarly biased assessments of their functional capacity.

The aim of this study was to investigate the relationship between subjective NYHA class determined by patient-physician interview and objective exercise capacity measured by VO_{2peak} during cardiopulmonary exercise testing in a heart failure patient population. Furthermore, we aimed to assess whether the relationship between subjective and objective functional capacity differs between patients who are adherent and nonadherent to pharmacotherapy for heart failure.

Methods

Data source

We used the data from the Level-CHF register, which contains information on patient adherence using a direct method: serum drug level testing.[13] We also enrolled patients who had undergone regular outpatient check-ups, including chemical adherence testing, at the specialized center of the university hospital. Data collection took place between February 2018 and February 2020, and was terminated by the COVID-19 epidemic, which prevented further recruitment of patients by limiting outpatient controls. All patients had CHF with a reduced ejection fraction (at least once during regular patient follow-up, with an ejection fraction of the left ventricle below or equal to 40%). All patients were clinically stable (no hospitalization for heart failure decompensation at all or at least 1 month after the last hospitalization) and had been taking unchanged test medication for at least 1 month prior to testing.

Cardiopulmonary exercise testing (CPET)

In addition to serum drug level testing, functional capacity was measured using VO_{2peak} by cardiopulmonary exercise testing on an electromagnetically braked stationary bicycle ergometer ERGOLINE E 900. Additionally, the ECG was recorded using a Cardiovit AT-104 PC ECG recorder, and the inhaled and exhaled gases were analyzed using a PowerCube Ergo analyzer. The tests were conducted us-

Table 1 – Comparison of the corresponding NYHA and Weber classification grades

NYHA class	Verbal expression of the NYHA class	Weber class	Verbal expression of the Weber class	VO_{2max} (MET, metabolic equivalent)
I	No limitation of physical activity	A	Little or no impairment	>20 ml/kg/min (>6 MET)
II	Slight limitation of physical activity	B	Mild to moderate impairment	16–20 ml/kg/min (4.5–6 MET)
III	Marked limitation of physical activity	C	Moderate to severe impairment	10–16 ml/kg/min (3–4.5 MET)
IV	Unable to carry on any physical activity without discomfort	D	Severe limitation	<10 ml/kg/min (<3 MET)

MET – metabolic equivalent of task; NYHA – New York Heart Association; VO_{2max} – maximal oxygen consumption.

Table 2 – Clinical characteristics of the patients

Clinical characteristics	N = 170
Age (mean, IQR)	59 (50–67)
Sex	Female 19.4%, male 80.6%
Fully adherent	136 (80%)
Partially nonadherent	24 (14%)
Completely nonadherent	10 (6%)
Ejection fraction of left ventricle (mean, IQR)	35% (25–42%)
Blood pressure systolic/diastolic (mmHg)	127.5 (17.5) / 78.1 (11.1)
Resting heart rate (beats/min)	71 (14)
NT-proBNP (pg/ml) (mean, IQR)	1209 (185–1222)
Diabetics	47 (28%)
Ischaemic cardiomyopathy	59 (35%)
Dilated cardiomyopathy	88 (52%)
Both ischaemic and dilated cardiomyopathy	10 (6%)
Other diagnoses	13 (8%)
Weber class	
Weber A	25 (15%)
Weber B	42 (25%)
Weber C	68 (40%)
Weber D	35 (21%)
NYHA class	
NYHA 1	28 (16%)
NYHA 1–2	26 (15%)
NYHA 2	57 (34%)
NYHA 2–3	20 (12%)
NYHA 3	36 (21%)
NYHA 3–4	2 (1%)
NYHA 4	1 (1%)
CPET characteristics	
Maximal heart rate (beats/min)	130 (28.4)
Maximal blood pressure systolic/diastolic (mmHg)	151,6 (29.7) / 82 (17)
VO_{2peak} (ml/kg/min)	14.8 (5.2)
Respiratory exchange ratio (RER)	1.1 (0.1)
VE/VCO_2	31.6 (6.2)
Metabolic equivalent (MET)	4.7 (1.5)
Power (W)	118.2 (88–146.25)
Relative power (W/kg)	1.4 (0.96–1.525)

CPET – cardiopulmonary exercise testing; IQR – interquartile range; MET – metabolic equivalent of task; NYHA – New York Heart Association; VO_{2max} – maximal oxygen consumption. Data are N (%) or mean (± standard deviation, or interquartile range, where more appropriate).

ing a modified Bruce protocol (STEEP protocol).[14] Maximal effort was defined as a respiratory exchange ratio (RER) more than 1.05. VO_{2peak} was defined as the highest 30-second average oxygen uptake in the last minute of the test.

Serum drug level testing (SDL)

We tested adherence by measuring the serum levels of angiotensin-converting enzyme inhibitors (ACEi), angiotensin receptor blockers (ARB), angiotensin-receptor-neprilysin inhibitors (ARNI), beta-blockers, and mineralocorticoid receptor antagonists (MRA). Other drugs were not measurable using our method. Sample analysis was performed using high-performance liquid chromatography coupled with tandem mass spectrometry (more information on the method is available in the online supplementary material). All patients without detectable serum drug levels for at least one medication that should be regularly used were considered nonadherent. Subsequently, the data were statistically analyzed.

Statistical analysis

Data preparation was performed using R programming language. Visualization was performed using ggplot2 package.[15] Association between VO_{2peak} and subjective NYHA class was assessed using a Bayesian cumulative ordinal model with the logarithm of the VO_{2peak} as a predictor and fitted with the brms package.[16] To evaluate the differences between adherent and nonadherent patients, we included both the main effect of adherence and interaction with VO_{2peak}. Since clinicians relatively frequently classified patients into transitional NYHA classes (NYHA 1–2, NYHA 2–3, NYHA 3–4) those are included in the model with the assumption that patients assigned a transitional class will, on average, have a VO_{2peak} somewhere between those of the neighboring standard NYHA classes. The full code to reproduce the analysis and the compiled report with additional details is available in the supplementary material.

Ethical considerations

Our study was based on data from the LEVEL-CHF registry, the creation and statistical analysis of which were approved by the ethics committee of Olomouc University Hospital. All participants were over 18 years old and signed an informed consent form before enrolment in the study. This study was designed in accordance with the latest Declaration of Helsinki.

Results

The study included 170 patients, whose clinical characteristics are shown in Table 2. The mean age of the patients was 59 years and 137 (80%) were men. The mean left ventricular ejection fraction (LVEF) was 35%. A total of 136 (80%) patients were fully adherent to drug treatment. 24 (14%) patients adherent to all but one medication, and 10 (6%) were completely nonadherent to their drugs. The percentage of each drug group is shown in Table 3.

Table 3 – Percentage representation of each drug group and corresponding adherence

	Percentage of users	Adherent
ACEi	54%	84%
ARB	10%	86%
ARNI	21%	100%
RAAS blockers combined	85%	88%
BB	95%	88%
MRA	79%	91%

ACEi – angiotensin converting enzyme inhibitors; ARB – angiotensin receptor blockers; ARNI – angiotensin receptor-neprilysin inhibitor; BB – beta-blockers; MRA – mineralocorticoid receptor antagonists; RAAS – renin-angiotensin-aldosterone system.

The trend between subjective and objective functional capacity

The relationship between subjective NYHA class and objective VO_{2max} is shown in Figure 1.

The subjective NYHA class and objective functional class by Weber based on VO_{2peak} were concordant only in 78 patients of 170 (46%), despite treating the transitional NYHA classes as concordant with both neighboring Weber classes (e.g., NYHA 2–3 was assumed concordant with both Weber B and C). More frequently, the objective functional class based on VO_{2peak} was higher than the subjectively reported NYHA class (82 patients, 48%), and less frequently lower (10 patients, 6%) (see Figure 2).

The agreement between cardiopulmonary exercise testing and subjective NYHA in our patients was largest for high values of VO_{2peak}, but even among the eight patients with VO_{2peak} > 25 mg/ml/kg, only four were assigned to the pure NYHA 1 class, while three were assigned NYHA 1–2 and one was assigned NYHA 2 subjective class. The variability in subjective NYHA classes was even larger for low VO_{2peak} values. Importantly, despite seeing many patients with a VO_{2peak} <10 ml/kg/min, only two of those patients reported subjective NYHA class 3–4 or 4. Therefore in these patients there is a major discrepancy between the subjective and objective functional class assessments. Additionally, the overall ranges of the observed VO_{2peak} values for subjective NYHA 1, 1–2, and 2 were almost identical (Fig. 1).

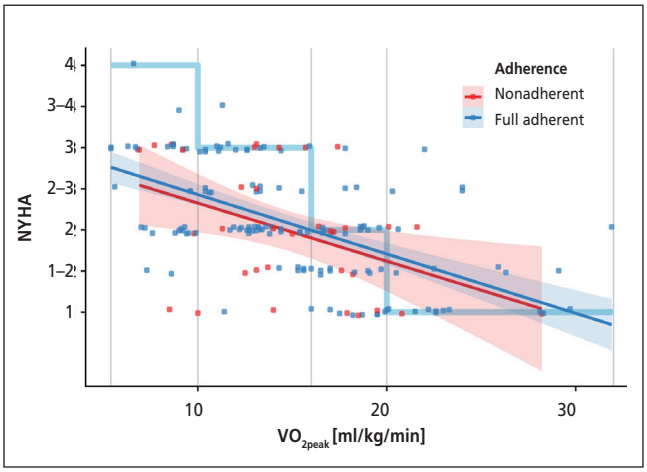

Fig. 1 – Subjective NYHA class compared to objective VO_{2peak}. Each dot is a patient. The vertical gray lines represent borders between different Weber classes. The thick light blue line shows expected output if NYHA based on VO_{2peak} exactly corresponded with subjective NYHA. Thin red and blue lines show linear trends fitted to each adherence category and the associated 95% confidence interval.

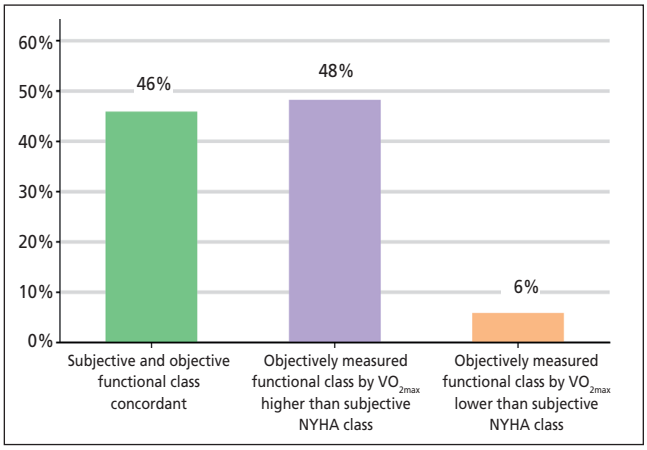

Fig. 2 – Proportions of patients with concordant and discordant subjective NYHA class and objective functional Weber class based on VO_{2peak}. Values were marked as concordant if the objective functional class value is equal to or falls within the range of the corresponding subjective NYHA.

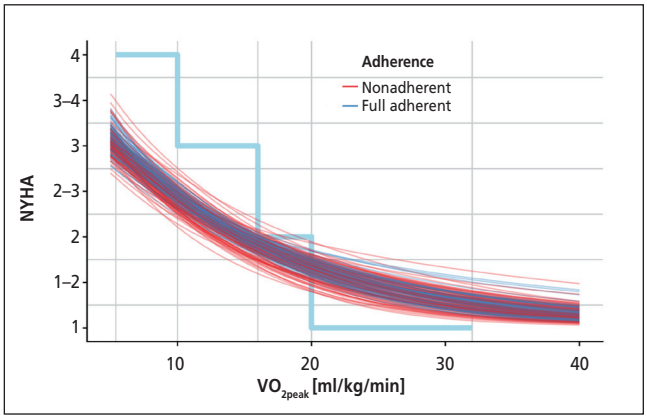

Fig. 3 – Average subjective NYHA as a function of VO_{2peak} and adherence. Each line is a posterior sample showing association between VO_{2peak} and average subjective NYHA as predicted by a cumulative ordinal model including the full interaction of logarithm of VO_{2peak} and adherence as predictors. The thick light blue line shows expected output if objective functional class based on VO_{2peak} exactly corresponded with subjective NYHA.

Association of functional class with adherence

The results of modelling subjective NYHA class as a function of both VO_{2peak} and adherence are shown in Figure 3. These data are consistent with nonadherent patients having both slightly higher and lower average subjective NYHA classes with the same VO_{2peak}. However, we can rule out substantial differences between adherent and nonadherent patients, as confirmed by the mean differences and 95% CI shown in Table 4.

Table 4 – Model-based differences in average subjective NYHA between adherent and nonadherent patients with the same VO_{2peak}

VO_{2peak}	Mean difference adherent to nonadherent	95% CI
10	0.04	[–0.64; 0.75]
20	0.14	[–0.5; 0.73]
30	0.09	[–0.73; 0.7]

CI – confidence interval; NYHA – New York Heart Association; VO_{2peak} – maximal oxygen consumption.
A difference of 1 would mean an average increase of one transitional class (e.g., from "1–2" to "2" or from "2–3" to "3").

Discussion

Our study showed that VO_{2peak} value acquired by cardiopulmonary exercise testing is an imperfect predictor of subjective NYHA score and vice versa and differs to a similar extent in both adherent and nonadherent patients. Therefore, we did not confirm our hypothesis that the disagreement between subjective and objectively measured functional classes would be higher in patients nonadherent to drug treatment for CHF.

Nonadherence to drug therapy occurs for several reasons and is a widespread problem in medicine that increases costs and leads to increased patient mortality and morbidity.[17–19] Patients with heart failure have a better adherence than those with arterial hypertension using the same types of drugs.[13] These drugs improve patient's prognosis and are essential medications for heart failure.[5]

Chemical adherence testing by measuring serum drug levels is a direct method of adherence assessment that is not dependent on the patient's willingness to tell the truth or the physician's ability to assess the level of adherence. Currently, chemical adherence testing is regarded as the gold standard for evaluating adherence.[20,21] Using liquid chromatography – tandem mass spectroscopy to detect serum drug levels is highly sensitive and reliable for detecting nonadherence.[22,23] In hypertensive patients serum drug level testing improves adherence and facilitates treatment.[24,25]

To our knowledge, this is the first study to use chemical adherence testing to investigate the relationship between objective and subjective functional capacities in patients with CHF.

The agreement between cardiopulmonary exercise testing and subjective NYHA class in both adherent and nonadherent patients was highest for high VO_{2peak} values and lowest for low VO_{2peak} values. It is relatively easy to decide whether a patient is NYHA class I or IV, but distinguishing neighboring classes, especially NYHA II and III, is more difficult, with a large potential for differences in classification depending on the symptoms reported by the patient at a given visit. For example, each person has a slightly different idea of what walking up a slight hill or up one flight of stairs means (some people do not walk upstairs at all), and the very concept of shortness of breath is subjective.[26]

Few studies have attempted to determine whether subjective and CPET-based objective functional capacity correlates in patients with heart failure. Most studies used a 6-minute walking test and did not measure VO_{2max}.[27] In general, studies report similar findings to ours that NYHA II and III significantly overlap according to VO_{2max}. Dunselman et al. found that 35% of NYHA II patients had a VO_{2peak} in the Weber A class range and 29% of NYHA III patients had a VO_{2peak} in the Weber D range.[28] Together 34% of patients with NYHA II or III were objectively classified into different functional categories. Contrary to our protocol, this study did not include patients in NYHA classes I and IV.

Genth et al. found that in patients with CHF, there was no correlation between VO_{2peak} and NYHA class; however, there was a correlation between anaerobic threshold and NYHA class. The NYHA class II and III VO_{2peak} ranges did not differ significantly, but in NYHA class II patients, there was a significantly higher anaerobic threshold.[29] In patients with congenital heart disease and resulting heart failure, Das et al. found an overlap in the VO_{2peak} in every NYHA class. Average VO_{2peak} in NYHA III patients was 16.8±4.5 ml/kg/min, most of these patients should be in Weber B class. Similarly, the average VO_{2peak} in NYHA II was also higher than that in Weber B class, 21.1±5.5 ml/kg/min. There was no significant difference in the measured VO_{2peak} between patients with NYHA class II and III. However, between classes NYHA I and II, as well as NYHA I and III, the difference was significant. Patients with NYHA class IV were excluded.[30]

Bredy et al. proposed that NYHA class and VO_{2peak} are strongly indirectly correlated in adult patients with congenital heart diseases and that NYHA alone is a strong predictor of patient prognosis. The average NYHA I was in the very high VO_{2peak} range of 29±9.1 ml/kg/min; similarly, the NYHA II average was high (21±7.9 ml/kg/min), which is higher than the corresponding Weber B range. On the other hand, the NYHA III average was 14.6±5.9 which is within the corresponding Weber C range.[31] The largest meta-analysis by Lim et al., including 38 studies on 2645 patients, found a generally inverse relationship between VO_{2peak} and NYHA class, but there was significant heterogeneity within each NYHA class, which was speculated to be due to differing interpretations of NYHA classification by the authors of different studies.[27]

Limitations

With the current data, we cannot draw strong conclusions regarding the potential change in the association between subjective NYHA and VO_{2peak} between the adherent and nonadherent patient subgroups. However, we can rule out large differences (an average of half a NYHA category or more in either direction). The precision achieved was limited by the low number of nonadherent patients observed in the cohort.

Another limitation of this study is the small number of patients with subjective NYHA class IV, as patients in this category are not usually subjected to stress testing. Adherence to drug treatment was measured only once. It is possible that there is some intra-individual variability in medication use, and repeated measurements may yield different results.

Additionally, only a low percentage of women was included in the cohort. This may be related to the higher prevalence of heart failure with preserved ejection fraction in women, which was not the focus of our analysis. Another explanation may be the generally lower prevalence of ischemic cardiomyopathy in women, which was experienced by most of our patients who became university hospital patients after myocardial infarction.

Conclusion

Subjective and objective functional capacities of patients with heart failure differ, particularly at both ends of the spectrum. If we make clinical decisions based on NYHA class, it is necessary to indicate objective measurements more often in clinical practice. Additionally, the collapse of the VO_{2peak} into the corresponding NYHA categories leads to loss of information, and using the VO_{2peak} values directly is preferable.

Our data provide evidence of large differences in subjective-objective NYHA trends between adherent and nonadherent patients.

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Author contribution statement
A draft of the manuscript was written by the first author in cooperation with the author of the statistical section of the study. All co-authors had access to the data and participated in the study through data collection and critical manuscript review.

Conflict of interest
There are no relevant relationships with the industry and no competing interests to declare.

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Supplementary material

Serum drug level analysis

"For detection of beta-blockers, the blood samples (serum) were prepared by liquid-liquid extraction LLE). All analyses were carried out using a UHPLC UltiMate 3000 RSLC System (Dionex, Sunnyvale, A, SA) connected with a UHR-TOF Maxis Impact HD (Bruker Daltonics, Billerica, MA, USA). Chromatographic separations were performed at 40 °C on a reverse phase analytical column Acclaim S 120 (Thermo Fisher Scien-tific, Waltham, MA, USA). The chromatographic conditions were: injection volume 5 mL, flow rate 0.5 mL/min, gradient elution, total runtime 6 min. UHR-TOF Maxis Impact HD equipped with an electrospray-ionisation source (ESI) operated in the positive MS mode."[1]

"For detection of other drugs apart from beta-blockers, the blood samples (plasma) were mixed with a mixture of deuterated internal standards and precipitated by 0.3 mol/L $ZnSO_4$ in 70% methanol. The supernatant was dried under a nitrogen stream at 40 °C. The residue was then reconstituted with mobile phase (A/B, 9:1 (v/v)). All analyses were performed using high-performance liquid chromatography (Ultimate 3000, Dionex, Sunnyvale, CA) coupled with tandem mass spectrometry (API 4000 triple quadrupole, AB Sciex, Sunnyvale, CA). Chromatographic separation was carried out on an Acquity BEH C18 column (1.7 mm, 2.1 £ 50 mm, Waters, Milford) at 50 °C with a gradient of methanol (mobile phase B) and 28 mm ammonium formate buffer (pH .8, mobile phase A) at a flow rate of 0.4 mL/min. The total analysis time was 2.3 min. The injection volume was 5 mL. The detection was performed using a positive electrospray-ionization technique and in multiple reactions monitoring mode."[1]

References

1. Jelínek L, Václavík J, Ramík Z, et al. Directly Measured Adherence to Treatment in Chronic Heart Failure: LEVEL-CHF Registry. Am J Med Sci 2021;361:491–498.