In heart failure, it has been recognized that sympathetic hyperactivity occurs, which is well counteracted by beta-blockers. In addition, there is frequently parasympathetic deficiency, which in turn contributes to the deterioration of cardiac function. The aim of the study was to evaluate the parasympathetic function by the deep breathing test and to highlight the deficiency of this system in the heart failure patient. We conducted a descriptive cross-sectional study from March to August of 2019. Patients were subdivided into 2 groups: group 1 included 35 patients with chronic heart failure (left ventricular ejection fraction ≤49%) and group 2 (control group) included 32 patients without heart failure (left ventricular ejection fraction ≥50%). The exploration of the parasympathetic system in our patients was based on the deep breathing test. It revealed a vagal deficit in 60% of group 1 patients versus 20% of group 2 patients. This difference was statistically significant between the 2 groups with a p-value of 0.032 (<0.05). These results showed a significant vagal deficiency in heart failure patients and were in line with the literature. Therefore, vagal stimulation in patients with heart failure may be a good therapeutic option to improve symptoms and cardiac function as some studies have shown.

Introduction:

In heart failure (HF), there is an autonomic imbalance consisting of sympathetic hyperactivity and vagal deficiency, which is known to lead to further worsening of the heart failure prognosis [1]. For this reason, the inhibition of the activated sympathetic system with beta-blockers is recommended. There are fewer studies concerning parasympathetic deficiency versus sympathetic hyperactivity in heart failure. Therefore, its pathophysiology is less known, its diagnosis is not common and its treatment is not yet practiced despite some studies have demonstrated that vagal stimulation has beneficial effects on heart failure specifically on the improvement of quality of life and symptoms [2-3]. The aim of our study is to highlight the parasympathetic deficiency in the heart failure patient by evaluating the vagal response with the deep breathing test.
Material and Methods:
The study was a descriptive cross-sectional study over a period of 6 months from March to August of 2019. Patients were subdivided into 2 groups: group 1 included 35 patients with chronic heart failure (left ventricular ejection fraction \( \leq 49\% \)) and group 2 (control group) included 32 patients without heart failure (left ventricular ejection fraction \( \geq 50\% \)).

All patients were in sinus rhythm. We applied the deep breathing (DB) test to assess the vagal activity. This test evaluates changes in the instant heart rate (RR space variation on the electrocardiogram) that is provoked by “deep” breathing at 6 breaths/min. The test is performed in supine position and starts with a rest period that gives patient time to relax.

The beta-blockers and vasodilators were stopped in all patients before at least 48 hours of the DB test. All patients underwent a complete clinical examination, electrocardiogram, echocardiography and DB test.

Statistical analysis of results was performed using SPSS software.

Results:
The mean age was 57+/−9 years in group 1 and 53+/−4 years in group 2. We noted a slight male predominance in both groups, 56% in group 1 with a sex ratio of 1.17 and 61% in group 2 with a sex ratio of 1.21.

The most common cardiovascualar risk factor in both groups was smoking. In group 1, diabetes and obesity were second only to smoking, then obesity and dyslipidemia (Table 1). The difference in cardiovascular risk factors between the two groups was statistically significant for smoking (p-value: 0.043) and hypertension (p-value: 0.003).

Table 1: Description of cardiovascular risk factors in both groups.

| Cardiovascular risk factor | Group 1 n=35 | Group 2 n=32 | p-value |
|----------------------------|--------------|--------------|---------|
| Chronic smoking            | 17 (48%)     | 13 (40%)     | 0.043   |
| Diabetes                   | 12 (34%)     | 9 (28%)      | 0.7     |
| Hypertension               | 8 (22%)      | 4 (12%)      | 0.03    |
| Dyslipidemia               | 7 (20%)      | 9 (28%)      | 0.54    |
| Android obesity            | 12 (34%)     | 10 (31%)     | 0.5     |

All patients in group 2 (control group) were asymptomatic except 3 patients with extracardiac symptoms including arthralgia, gastric ulcer and chronic low back pain of undetermined cause.

In group 1, according to the NYHA classification of dyspnea, 5 patients had stage I, 21 patients had stage II, 9 patients had stage III, and no patients had stage IV.

In group 1, two patients reported atypical precordialgia, 2 patients had palpitations and 1 patient had a syncopal episode. In the same group, 22 patients had no signs of heart failure (HF), 6 patients had isolated right-sided signs of HF, 3 patients had left-sided signs of HF, and 4 patients had global signs of HF.

In group 2, the echocardiography revealed a moderate left ventricular hypertrophy with slight dilatation of the left atrium in 2 patients. All patients had normal LVEF \( \geq 50\% \) with no significant valvulopathy. However, in group 1, 23 (66\%) patients had LVEF between 35 % and 49% (Fig 1), 3 (8\%) patients had severe aortic insufficiency and 2 (5\%) patients had severe mitral insufficiency.

The etiologies of heart failure in group 1 in descending order were ischemic heart disease (54\%), valvular disease, primary dilated cardiomyopathy and hypertensive cardiomyopathy. (Fig 2). In Group 1 patients, evaluation of parasympathetic activity by deep breathing test showed that 21 patients (60\%) had vagal deficiency and 14 patients had normal vagal response (Fig 3). However, in group 2, only 7 patients (21\%) had vagal deficiency. Among these patients, 4 were hypertensive and 1 was diabetic.

The difference of deep breathing test between the 2 groups was statistically significant with a p-value of 0.032.
Figure 1: Distribution of Group 1 patients according to LVEF.

Figure 2: Etiologies of heart failure in group 1 patients.

Figure 3: Prevalence of vagal deficiency in group 1 patients.
Discussion:

The concept of autonomic reflex dysfunction in human heart failure emerged from the demonstration by Eckberg et al of attenuated bradycardia in response to a drug-induced rise in systolic arterial pressure[4]. Regardless of the etiology of heart failure, there are an almost constant parasympathetic deficiency and sympathetic hyperactivity that evolve over time[5]. Indeed, when the heart dilates, vagal and sympathetic afferent cardiac fibers increase their firing, and this afferent sympathetic excitation leads to the tonic and reflex inhibition of cardiac vagal efferent activity. Therefore, heart failure should be considered as a disorder of autonomic and myocardial function [6].

The results of our study showed a significant vagal deficiency in heart failure patients compared to patients without heart failure. This result concords with many studies. Nolan et al conducted a study in heart failure patients, using 24 hour Holter-ECG recordings, and demonstrated that there was a significant linear correlation between the parameters of heart rate variability in relation to vagal deficiency and the severity of left ventricular dysfunction [7]. Musialik’s Polish study also compared the rate of left ventricular dysfunction and parameters of heart rate variability in heart failure patients and concluded that there was a significant correlation between these two parameters [8].

Vagal deficiency is certainly found in heart failure due to ventricular dysfunction, but there are other situations that favour it independently of ventricular function such as diabetes [9], hypertension [10], smoking [11], obesity [12], dyslipidemia [13], sedentary lifestyle [14] and some cardiac diseases such as ischemic heart disease [15], dilated cardiomyopathy [16], and hypertensive cardiomyopathy.

In group 2 (control group) of our study, 4 diabetic patients and one hypertensive patient had vagal deficiency, which is in line with the literature data [10-15].

Therefore, parasympathetic deficiency in heart failure is the result of ventricular dysfunction. This deficiency is favored or aggravated by the existence of cardiovascular risk factors and some etiologies of heart failure.

Vagus nerve stimulation (VNS) to restore vagal activity in heart failure has garnered increasing interest in recent years. The results of trials were promising. The Autonomic Neural Therapy to Enhance Myocardial Function in Heart Failure (ANTHEM-HF) study evaluated the use of a VNS system in patient with HF [17]. In this study, there were statistically significant improvements in the primary efficacy endpoints of LVEF and left ventricle end-systolic volume (LVESV) as well as the secondary efficacy endpoints of left ventricle end-systolic diameter (LVESD), heart rate variability and 6-minute walk test (6MWT). Subsequent 12-month follow-up on 49 of the initial 60 patients showed that improvements persisted during longer follow-up and that the device implantation remained safe. Two other studies, NECTAR-HF Trial [2] and INOVATE-HF Trial [3], showed improvement in NYHA class of dyspnea, patient quality of life and 6-minute walk test, but no improvement in mortality.

Consequently, vagal stimulation could enhance the functional prognosis as well as quality of life of heart failure patients and it maybe as effective as sympathetic inhibition. However, there is still no consensus or validated protocol regarding this new therapeutic approach.

Conclusion:

Heart failure is associated with significant morbidity and mortality despite the use of medical therapy that targets, in part, the neurohormonal axis. This disease is characterized by autonomic imbalance with increased sympathetic activity and withdrawal of parasympathetic activity which contribute to the deterioration of cardiac function. Therefore, it’s necessary to carry out more studies on vagal deficiency to target it in the treatment of heart failure, especially that some trials revealed a promising effect of vagal stimulation.

References:

1. Floras JS, Ponikowski P. The sympathetic/parasympathetic imbalance in heart failure with reduced ejection fraction. Eur Heart J 2015; 36: 1974–1982.
2. ZannadF, DeFerrariG, M, TuinenburgA, E et al. Chronic vagal stimulation for the treatment of low ejection fraction heart failure: results of the NERual Cardiac TherApioR Heart Failure (NECTAR-HF) randomized controlled trial. Eur Heart J. 2015 Feb 14; 36(7): 425–433.
3. Gold MR, Van Veldhuisen DJ, Hauptman PJ et al. Vagus Nerve Stimulation for the Treatment of Heart Failure: The INOVATE-HF Trial. J Am Coll Cardiol. 2016 Jul 12;68(2):149-58.
4. Eckberg DL, Drabinsky M, Braunwald E. Defective cardiac parasympathetic control in patients with heart disease. N Engl J Med 1971;285:877–883.
5. P.J. Schwartz, G.M. Ferrari. Sympathetic-parasympathetic interaction in health and disease: abnormalities and relevance in heart failure. Heart Fail Rev, 16 (2011), pp. 101-107.
6. Floras JS. Sympathetic nervous system activation in human heart failure: clinical implications of an updated model. J Am Coll Card 2009;54:375–385.
7. Nolan J, Flapan AD, Capewell S, MacDonald TM, Neilson JM, Ewing DJ. Decreased cardiac parasympathetic activity in chronic heart failure and its relation to left ventricular function. Br Heart J. 1992;67:482–485.
8. Musialik-Lydka A, Sredniawa B, Pasyk S. Heart rate variability in heart failure. Kardiol Pol. 2003 Jan;58(1):10-6.
9. Lefrandt JD, Smit AJ, Zeebregts CJ et al. Autonomic dysfunction in diabetes: a consequence of cardiovascular damage. Curr Diabetes Rev. 2010 Nov;6(6):348-58.
10. Fagard RH, Stolarz K, Kuznetsova T et al. Sympathetic activity, assessed by power spectral analysis of heart rate variability, in white-coat, masked and sustained hypertension versus true normotension. J Hypertens. 2007 Nov;25(11):2280-5.
11. Erdem A, Ayhan SS, Öztürk S et al. Cardiac autonomic function in healthy young smokers. Toxicol Ind Health. 2015 Jan;31(1):67-72.
12. Karason K, Mølgaard H, Wikstrand J, Sjöström L. Heart rate variability in obesity and the effect of weight loss. Am J Cardiol. 1999 Apr 15;83(8):1242-7.
13. Doncheva NI, Nikolova RI, Danev SG. Overweight, dyslipoproteinemia, and heart rate variability measures. Folia Med (Plovdiv). 2003;45(1):8-12.
14. Tuomainen P, Peuhkurinen K, Kettunen R, Rauramaa R. Regular physical exercise, heart rate variability and turbulence in a 6-year randomized controlled trial in middle-aged men: the DNASCOS study. Life Sci. 2005 Oct 7;77(21):2723-34.
15. Carpeggiani C, L’Abbate A, Landi P et al. Early assessment of heart rate variability is predictive of in-hospital death and major complications after acute myocardial infarction. Int J Cardiol. 2004 Sep;96(3):361-8.
16. Malfatto G, Brunzi G, Grittì S et al. Different baseline sympathovagal balance and cardiac autonomic responsiveness in ischemic and non-ischemic congestive heart failure. Eur J Heart Fail. 2001;3:197–202.
17. Premchand RK, Sharma K, Mittal S, Monteiro R et al. Extended Follow-Up of Patients With Heart Failure Receiving Autonomic Regulation Therapy in the ANTHEM-HF Study. J Card Fail. 2016 Aug;22(8):639-42.