Original Article

Correlation between Pulse Pressure and Sub-maximal Functional Capacity in Patients with Heart Failure with Preserved Ejection Fraction

Gustavo Matas Kern,[1] Luiz Claudio Danzmann,[1] Leticia Kunst,[1] Ludmila Limpias Terrazas Binkowski,[1] Carla Alessandra Smiderle[1]

Universidade Luterana do Brasil (ULBRA),[1] Canoas, RS – Brazil

Abstract

Background: **Heart failure with preserved ejection fraction (HFpEF) is characterized by diastolic dysfunction, as well as alterations in ventricular filling and remodelling. This change in diastolic function without reduced ejection fraction is manifested as exercise intolerance, and arterial stiffness, measured by pulse pressure, is considered an independent predictor of functional capacity.**

Objective: **To evaluate the correlation between sub-maximal functional capacity and pulse pressure (PP) in patients with HFpEF.**

Methods: **Patients with HFpEF performed the 6-minute walk test (6MWT) in a 45-meter hallway at the University Hospital. Patients were instructed to walk at a speed consistent with their daily activities. Their vital signs were monitored, and the Borg scale was applied for symptoms such as dyspnea and fatigue. Blood pressure was measured at rest. PP was estimated using the formula PP = systolic blood pressure − diastolic blood pressure, with 65 mmHg as the cutoff point.**

Results: **We observed a difference of 120.5 ± 43.97 meters between the mean distances walked during the 6MWT between the groups with increased and normal PP (294.5 ± 111.3 m versus 415.4 ± 105.3 m, $p = 0.01$). Pearson's test demonstrated a slight inverse correlation between PP values and the distance walked by patients during the 6MWT ($r = -0.4$, $p = 0.049$).**

Conclusion: **There was a reduction in sub-maximal capacity in patients with increased PP, as shown by the slight inverse correlation between PP and distance walked during the 6MWT.**

Keywords: **Heart Failure; Vascular Stiffness; Blood Pressure.**

Introduction

Heart failure (HF) is a frequent syndrome, and it is one of the main reasons for hospitalization due to cardiovascular causes.[1,2] Despite advances in therapy, HF remains a serious clinical syndrome with significant risks of hospitalization due to heart decompensation, disease, and death.[2,3] It is estimated that, on average, 1% to 3% of the population has HF,[3] with a prevalence that significantly increases with advancing age.[2,3]

HF can be classified according to ejection fraction (reduced, slightly reduced, preserved, or improved), the severity of symptoms (New York Heart Association [NYHA] functional classification), and the time and progression of the disease (different stages).[4]

The pathophysiology of heart failure with preserved ejection fraction (HFpEF) involves increased left ventricular and blood vessel stiffness. Arterial stiffening correlates with end-diastolic pressure and cardiac output reserve. In the healthy heart, cardiac and vascular reserves maintain efficient ventricular-arterial coupling during exercise. In HFpEF, however, contractile and vascular reserve deficiencies lead to abnormal ventricular-arterial coupling.[3]

Pulse pressure (PP) is used as an indicator of arterial stiffness, and increased PP has been considered an independent risk factor for cardiovascular events[5] and progression of atherosclerosis in the aorta and carotid arteries.[6] Several genetic and environmental factors cause structural changes in the arterial wall, leading to a reduction in its compliance and consequent increase in systolic blood pressure (BP), translating to increased PP.[7] Important factors that determine PP include left ventricular ejection volume and velocity, elastic properties of large arteries, and peripheral vascular resistance.[5]

The objective of this study was to evaluate the correlation between sub-maximal functional capacity, measured by the 6-minute walk test (6MWT), and peripheral arterial PP in patients with HFpEF treated at the HF outpatient clinic of the University Hospital of Canoas (HUC, abbreviation in Portuguese), Rio Grande do Sul, Brazil.

Materials and Methods

This is a retrospective observational study, with sample data were collected between the years 2011 and 2012, including

Mailing Address: Gustavo Matas Kern •
ULBRA - Rua Coronel Bordini, 1130 apt. 401. Postal Code 90440-003, Porto Alegre, RS - Brazil
E-mail: gukern94@gmail.com
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patients monitored at the HF outpatient clinic of the HUC, all of whom had HF, according to the 2021 criteria of the European Society of Cardiology,[8] with ejection fraction greater than or equal to 50% and diastolic dysfunction. Patients with ejection fraction below 50%, congenital heart disease, valve insufficiency with hemodynamic repercussions, pacemaker and/or implantable cardioverter-defibrillator were excluded. Patients with atrial fibrillation were also excluded due to greater difficulty in measuring PP.

The following variables were analyzed: demographic characteristics, NYHA functional class, sedentary lifestyle, tobacco use, diagnosis of diabetes mellitus and systemic arterial hypertension, left ventricular ejection fraction, distance walked during the 6MWT, BP, symptoms during and after the test, and medications in use. Data were collected from a database created through collection instruments.

The subjects of the sample underwent the 6MWT. No changes were made to the prescription of usual medications to perform the test. The 6MWT was performed in a 45-meter-long corridor at the University Hospital of the Lutheran University of Brazil (ULBRA, abbreviation in Portuguese). Patients were instructed to walk at a comfortable speed, consistent with their daily activities. Words of encouragement were used. Patients were monitored regarding heart rate, respiratory rate, and BP. The Borg scale of predictive value for symptoms such as dyspnea and fatigue was applied.

BP was measured in the right arm, at rest, prior to the 6MWT, with a duly calibrated Missouri manual brachial cuff sphygmomanometer for adults. PP was estimated using the formula PP = systolic BP – diastolic BP. The cutoff point used for PP value was 65 mmHg.[9] Although pulse wave velocity is considered the gold standard for measuring arterial stiffness,[10] this parameter was not used in this study due to the fact that appropriate equipment was unavailable.

Data were processed using SPSS software, version 19.0. Categorical variables were analyzed as percentages. Based on the continuous variables, the mean and standard deviation were calculated. The association between the distance walked and PP was evaluated using Pearson's correlation coefficient. Student's t test for independent samples was used to evaluate the difference in the distance walked between patients with normal and altered PP. P values < 0.05 were considered statistically significant.

The collection instruments used in this study had previously received approval from the ULBRA Research Ethics Committee (2010/207 H) under an umbrella project for vascular investigation in HF entitled "Association between heart failure with preserved ejection fraction and the ankle-brachial index". All patients in the sample signed the free and informed consent form.

Results

A total of 25 participants were allocated; all patients were from the HUC HF outpatient clinic. As shown in Table 1, the majority of the patients in the study population were women (84%), with a mean age of 65 ± 12.7 years, and the majority had obesity. All participants had ejection fraction > 50%, with a mean of 66.7% ± 8% (Table 2). Regarding the etiology of HF, 56% had HF with no history of ischemic events. The main medications in use were angiotensin-converting enzyme inhibitors/angiotensin receptor blockers (92%), diuretics (80%), beta-blockers (56%), calcium channel antagonists (48%), vasodilators (32%), and spironolactone (16%). None of the patients in the sample were using digitalis or antiarrhythmics (Table 3), keeping in mind that the study was carried out between 2011 and 2012.

Table 1 – Sample characteristics (categorical variables)

Variable	N	%
Female sex	21	84.0
White ethnicity	23	92.0
Diabetes mellitus	11	44.0
Systemic arterial hypertension	24	96.0
Sedentary lifestyle	20	80.0
History of tobacco use	9	36.0
NYHA I or II	20	80.0
NYHA III or IV	5	20.0
Increased pulse pressure	10	40.0
Non-ischemic etiology	14	56.0

NYHA: New York Heart Association functional class.

Table 2 – Sample characteristics (continuous variables)

Variable	Mean ± standard deviation
Ejection fraction	66.7 ± 8.0
Age	65 ± 12.7
Body mass index	33.26 ± 5.24
Distance walked on the 6MWT	367 ± 121.5
Systolic blood pressure	138.8 ± 17.1
Diastolic blood pressure	79.6 ± 11.5

6MWT: 6-minute walk test.

Regarding symptomatology of HF, 5 patients (20%) were in NYHA functional class I; 15 (60%) were in class II; 3 (12%) were in class III, and only 2 patients (8%) were in class IV. Regarding lifestyle, the majority of the sample was sedentary (80%) and non-smokers (64%). In relation to the comorbidities studied, almost all patients had systemic arterial hypertension (96%), and nearly half of the sample had diabetes mellitus (44%).

The average distance walked during the 6MWT was 367 ± 121.5 meters. In relation to BP, mean resting systolic and diastolic pressures were 138.8 ± 17.1 mmHg and 79.6 ± 11.5 mmHg, respectively. PP was above the cutoff point (> 65 mmHg) in 40% of the patients.

During the 6MWT, only 8 patients required a break; dyspnea was the main reason (68.5%), followed by fatigue (37.5%), chest burning (12.5%), palpitation (12.5%), and pain in lower limbs (12.5%). After the test, including patients who did not pause during the test, the main complaints were hip, leg, or calf pain (Table 4).

Table 3 – Antihypertensive medications used by the sample

Variable	N	%
Beta blocker	14	56.0
ACEI/ARB	23	92.0
Diuretics	20	80.0
Spironolactone	4	16.0
Vasodilators	8	32.0
Calcium channel antagonists	12	48.0

ACEI/ARB: angiotensin-converting enzyme inhibitors/angiotensin receptor blockers.

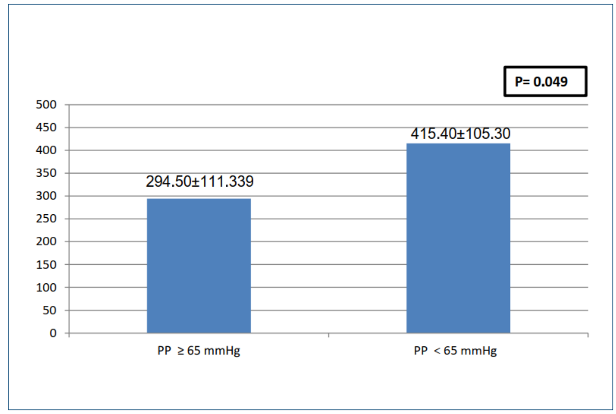

Figure 1 – *Mean distance walked during the 6-minute walk test according to pulse pressure. PP: pulse pressure.*

Table 4 – Description of symptoms during and after the 6-minute walk test

Variable	Category	N (%)
Break	No	17 (68%)
	Yes	8 (32%)
Reason for the break	Chest burning	1 (12.5%)
	Dyspnea	5 (62.5%)
	Lower limb pain	1 (12.5%)
	Fatigue	3 (37.5%)
	Palpitation	1 (12.5%)
Symptoms after 6MWT	None	9 (36%)
	Chest pain	8 (32%)
	Hip, leg, or calf pain	9 (36%)
	Dyspnea	5 (20%)
	Others	2 (8%)

6MWT: 6-minute walk test.

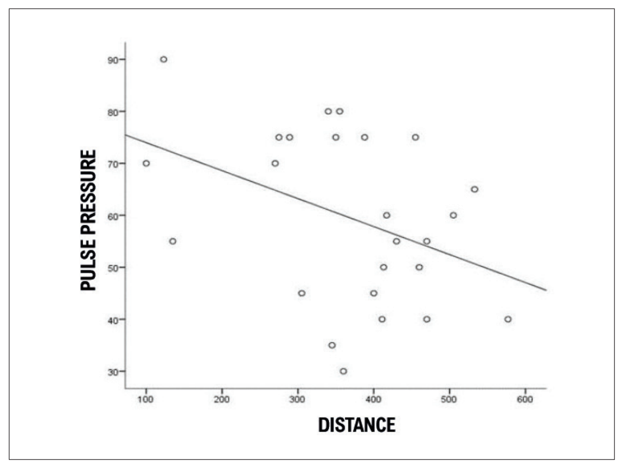

Figure 2 – *Pearson's correlation between pulse pressure and distance walked during the 6-minute walk test [P1].*

In relation to the distances walked during the 6MWT, a difference was observed between the groups with increased and normal PP (294.5 ± 111.3 m versus 415.4 ± 105.3 m, p = 0.01) (Figure 1). Additionally, Pearson's test showed a slight statistically significant inverse correlation between PP values and the distance walked, in meters, by patients during the 6MWT ($r = -0.4$, $p = 0.049$) (Figure 2).

Discussion

This study has demonstrated a slight, statistically significant, inverse correlation between the PP value and the functional capacity of patients with HFpEF, based on the distance walked during the 6MWT. A difference of 120.9 meters was observed between participants with HFpEF and increased PP, compared to the group without increased PP. This has provided evidence that there is an inversely proportional correlation between PP and distance walked.

Elevated PP is an established marker of adverse outcomes in healthy individuals, as well as in patients with certain types of cardiovascular disease, especially those with hypertension.[5] More recently, lower PP has emerged as an independent predictor of mortality in patients with HF; this has been demonstrated in patients across the spectrum of symptom severity and in patients with acute and chronic HF.[11] Furthermore, patients with HFpEF more frequently have a history of hypertension than patients with HF with reduced ejection fraction; therefore, they more frequently have elevated PP.[5,11] The impact of PP in patients with HFpEF is not as well established as in cases of HF with reduced ejection fraction; however, Wei et al.[12] underscore that, in patients with HFpEF, PP can assist in further investigation of the development of HFpEF, supporting preventive strategies aimed at controlling pulsatility and BP.

Ferreira et al. demonstrated the impact of sub-maximal functional capacity on the prognosis of HF. In their study, approximately 80% of deaths were correlated with the distance walked during the test, moderate to severe mitral regurgitation, age, and ejection fraction.[13] According to the results, increased risk of death was observed mainly in patients unable to walk 200 meters, and distances greater than 200 meters did not seem to provide additional information on mortality risk.[14] The study showed that the distance walked during the 6MWT was a reliable prognostic indicator of mortality for patients with HF ($p < 0.0001$).

Studies have shown that the functional capacity of patients with HFpEF during the 6MWT is related to PP. The study by Kang et al.[15] showed the existence of a correlation between arterial stiffness and diastolic HF, in which patients with diastolic HF had higher ankle-brachial pulse wave velocity, a reliable marker of this stiffness (1,670.5 cm/s, $p < 0.01$). According to Mottram et al.,[16] in patients with diastolic dysfunction, arterial compliance is strongly related to PP ($r = -0.74$, $p < 0.001$), making it an independent parameter in predicting this dysfunction ($\beta = 0.458$, $p = 0.001$).[16] High PP in patients with HFpEF was correlated with increased pulse wave velocity (the gold standard for measuring arterial stiffness).

Laskey et al.[17] evaluated the association between PP and adverse outcomes at one year in patients hospitalized for HF. In patients with HFpEF, there was a significant association between PP and mortality, with risk increasing as PP increased, although the magnitude of risk was significantly affected by systolic BP. The study shows that the association is significant when PP values are above 50 mmHg; when systolic BP > 140 mmHg, the association was even more unfavorable ($p = 0.0041$).

Regarding the relationship between PP values and functional capacity, our data demonstrated that, in patients with PP ≥ 65 mmHg, the distance walked during the 6MWT was significantly lower (294.50 ± 111.339 m versus 415.40 ± 105.30 m, $p = 0.045$). In a study observing functional capacity by NYHA classes in HFpEF groups, Tokitsu et al.[18] found that PP values in patients with HF in NYHA class II were different from those in NYHA class III/IV. Patients with relatively more severe HFpEF had more extreme PP values, both lower and higher. Patients with PP values lower than 45 mmHg and PP values greater than 75 mmHg had significantly higher frequencies of HF-related symptoms than those with PP values ranging from 45 to 74 mmHg.[16] Moreover, this study found that patients with HFpEF with PP values less than 45 mmHg and PP values greater than 75 mmHg had notably higher frequencies of cardiovascular and HF-related events than those with PP values ranging from 45 to 74 mmHg.[18] In patients with NYHA III, high PP is related to a worsening of functional capacity. Guazzi et al. demonstrated that severe diastolic dysfunction is related to worsening of exercise capacity in patients with HFpEF.[19]

Elevated PP is associated with advanced age, female sex, history of hypertension, diabetes mellitus, elevated systolic BP, and higher ejection fraction.[20] Increased arterial stiffness, associated with increased afterload, causes premature return of pulse wave, which increases cardiac work and myocardial oxygen demand. Thus, increased PP leads to cardiac hypertrophy[14] and greater susceptibility to ischemia, even in the absence of coronary stenosis.[21] An increase of 10 mmHg in PP leads to a 14% increase in the risk of developing HF.[22]

HFpEF is a syndrome characterized by significant changes in ventricular filling and atrioventricular and vascular remodeling. These cardiac and vascular functional alterations correlate with patients' common morbidities: essential arterial hypertension, diabetes mellitus, overweight, and advanced age.[23] The sample was almost entirely composed of patients with hypertension, with a high prevalence of diabetes and advanced age.[18] In these patients, increased arterial stiffness has been reported as an independent predictor of cardiovascular events.[20] Kawaguchi et al.[24] reported that HFpEF is characterized by ventricular and systolic arterial stiffening in addition to that associated with aging and hypertension, resulting in cardiac diastolic dysfunction.

Al Rifai et al.,[25] based on the pulse pressure stress index (P2SI), showed that there is a significant inverse relationship between change in PP on exertion (measured by P2SI) and the risk of HF and all-cause mortality. That study also suggested that patients with low P2SI should be considered for more aggressive risk factor control in order to reduce the risk of subsequent HF, particularly for patients with stage A disease.

Dhakal et al.,[26] when performing maximum incremental cardiopulmonary exercise testing with invasive hemodynamic monitoring in 104 patients with symptomatic NYHA II to IV HF, concluded that impaired peripheral oxygen extraction, which reflects intrinsic abnormalities in skeletal muscle or peripheral microvascular function, was the predominant limiting factor to exercise capacity in 40% of patients with HFpEF. They also observed a close relationship between these findings and the increase in systemic BP during exercise.

In patients with HF, with both preserved and reduced ejection fraction, there is evidence that arterial stiffness is related to changes in functional capacity. This occurs through a decrease in cardiac reserve, leading to an exaggerated increase in left ventricular filling pressure during exercise.[10] The Aldo-DHF study[14] demonstrated an independent association between increased left ventricular filling pressure, assessed using the E/E' index, and increased PP.

In agreement with these data, the analyses of this study demonstrated the existence of an inverse correlation between the distance walked during the 6MWT and PP, used as an index of systemic arterial stiffness, in the patients of the sample. This result strongly suggests that the process of increased left ventricular afterload leads to a change in the function of anterograde ventricular filling and emptying, which can also be considered an alteration in functional ventricular-arterial coupling. In other words, patients with greater arterial stiffness would have difficulty adapting cardiac output to situations of greater demand and, therefore, a lower functional capacity. Although no correlation was found between left ventricular ejection fraction and 6MWT distance, it was possible to observe a correlation between the exercise measurements examined with estimates of left ventricular filling pressures. Taken together, these observations suggest that the 6MWT is a valid exercise testing modality to objectively assess clinical status and degree of exercise limitation.

The main limitation of this study is related to the small number of participants. Thus, it is not possible to establish a cause-and-effect relationship between PP and distance walked, making PP only a marker of severity and not the cause of the shorter distance walked. For the same reason, it was not possible to make a statistically significant comparison between HFpEF subgroups with ejection fraction from 50% to 60% and ejection fraction > 60%, since both ranges have pathophysiological differences.[27] Regarding the differences in our sample in relation to contemporary treatment of HFpEF, it should be noted that, when the study was conducted, no evidence had been published on the efficacy of sacubitril/valsartan or SGLT2 inhibitors in the population with HFpEF.

Conclusion

In a sample of patients with HFpEF, we observed a significantly lower sub-maximal capacity in patients with PP ≥ 65 mmHg. Furthermore, we found a slight inverse correlation between PP and distance walked during the 6MWT.

Author Contributions

Conception and design of the research, Acquisition of data, Statistical analysis and Obtaining financing: Danzmann LC; Analysis and interpretation of the data, Writing of the manuscript and Critical revision of the manuscript for important intellectual content: Kern GM, Danzmann LC, Kunst L, Binkowski LLT, Smiderle CA.

Potential conflict of interest

No potential conflict of interest relevant to this article was reported.

Sources of funding

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Study association

This study is not associated with any thesis or dissertation work.

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