Original articles

Restrictive left ventricular filling pattern as a strong predictor of depressed baroreflex sensitivity in heart failure

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Key words:
Baroreflex sensitivity; Diastolic dysfunction; Heart failure.

Background. **The aim of this study was to test the hypothesis that a restrictive left ventricular diastolic filling pattern, as an index of elevated pulmonary wedge pressure, would predict a depressed baroreflex sensitivity (BRS) in patients with chronic heart failure.**

Methods. **A total of 189 consecutive patients with an ejection fraction ≤ 40% at echocardiography, in sinus rhythm and clinically stable for at least 1 month in oral therapy, underwent clinical examination, echo-Doppler study and the phenylephrine test.**

Results. **The correlations between the NYHA functional class, echo-Doppler variables and BRS were weak, although significant (r ranging from -0.15 to 0.40). However, patients with a deceleration time < 140 ms as an expression of restrictive filling, compared to those with a deceleration time ≥ 140 ms, had a lower BRS (3 ± 4 vs 6 ± 4 ms/mmHg, p < 0.00001), a lower ejection fraction (20 ± 6 vs 28 ± 7%, p < 0.00001), greater left ventricular (end-diastolic volume index 137 ± 43 vs 113 ± 45 ml/m^2, p < 0.00001) and left atrial dimensions (25 ± 6 vs 20 ± 5 cm^2, p < 0.00001), more severe mitral regurgitation (3 ± 1 vs 2.3 ± 1, p < 0.00001) and were in a higher NYHA class (2.3 ± 0.6 vs 1.8 ± 0.5, p < 0.00001). Medications at the time of the study were similar in the two groups. At stepwise regression analysis, the deceleration time emerged as the most powerful independent predictor of a depressed BRS (< 3 ms/mmHg), followed by mitral regurgitation, age, and NYHA class (all data p = 0.0001).**

Conclusions. **In patients with chronic heart failure, the presence of a restrictive left ventricular filling pattern is highly predictive of autonomic derangement as expressed by low values of BRS.**

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Introduction

Depending on age heart failure occurs in 1 to 2% of the total population, and accounts for up to 5% of admissions to a general hospital[1]. Mortality is high: about 50% in 1 year for patients with advanced heart failure, and 50% in 5 years in those selected from the general population. The role of neurohormonal changes in the progression of heart failure is well established. In the early stages, activation of humoral systems apparently serves as a compensatory mechanism for the failing circulation; however, overshoot of such mechanisms may further depress cardiac function by increasing afterload. This leads to a vicious cycle of reflex neuroendocrine activation.

Theoretically, patients with a more compromised hemodynamic status should have a higher probability of presenting with a more pronounced autonomic derangement. This is easily detectable by simple analysis of heart rate variability, as an index of vagal tone, and of baroreflex sensitivity (BRS), as an index of the vagal response to sudden variations in blood pressure[2].

The aim of the present study was to verify the hypothesis that a restrictive left ventricular filling pattern at Doppler echocardiography, as an index of diastolic dysfunction and elevated pulmonary wedge pressure, can predict a depressed BRS in patients with chronic heart failure.

Methods

Study group. One hundred eighty-nine consecutive patients with chronic heart failure

(167 men, 22 women, mean age 56 ± 10 years) were enrolled on the basis of a left ventricular ejection fraction (EF) ≤ 40% at echocardiography, the presence of sinus rhythm, and clinical stability for at least 1 month with oral therapy at the time of the study. Those patients who had undergone coronary artery bypass within the previous 6 months or for whom echocardiographic images and Doppler recordings were inadequate as well as those who presented with atrial fibrillation, severe valvular stenosis and/or valvular cardiomyopathy, unstable angina pectoris or ischemia requiring revascularization, myocardial infarction during the previous 3 months or severe pulmonary disease were excluded from the study. None of the patients enrolled had clinical signs of central nervous impairment or dysautonomia. Thirty-five patients had a history of diabetes mellitus: all were metabolically compensated with insulin therapy or oral hypoglycemic agents, and none of them had clinical signs of peripheral neurologic involvement. All patients had symptomatic left ventricular dysfunction as defined by a previous unequivocal episode of heart failure. One hundred and forty-eight patients had ischemic cardiomyopathy and 41 patients idiopathic cardiomyopathy.

Study protocol. All patients underwent complete two-dimensional echocardiography and Doppler ultrasound examination and, within 3 days of these investigations, BRS evaluation.

All echocardiographic studies were performed with a Hewlett-Packard ultrasound system (model 77729-A or 77622-A, with 2.5 and 3.5 MHz probes); the examinations were recorded on tape, and then reviewed by a single cardiologist. The following data were registered during the orthogonal apical views: left ventricular volumes (area-length method according to data derived during the 4-chamber, 5-chamber, 2-chamber and 3-chamber apical views), EF derived from the standard equation (left ventricular end-diastolic - end-systolic volume/end-diastolic volume; mean value as calculated at the 4-chamber, 5-chamber, 2-chamber and 3-chamber apical views), maximal atrial area and mitral regurgitation, semiquantitatively graded at color-flow Doppler as absent, mild, moderate or severe (values ranging from 1 to 4). The mitral flow velocity was assessed at pulsed-wave Doppler during the apical 4-chamber view with the sample volume positioned between the tip of the mitral leaflets in diastole. The peak E and A wave transmitral flow velocities and the deceleration time of early filling were measured as previously described[3].

All patients underwent the phenylephrine test to assess BRS; they were studied in a fasting state and in a supine position, in the morning hours (9.00-12.00 a.m.). Prior to evaluation beta-blocker agents, nitrates and diuretics were discontinued (beta-blockers 72 hours and nitrates 24 hours before; the daily dosage of diuretics was postponed until the test had been completed). One electrocardiographic lead and the arterial blood pressure signal were simultaneously recorded by means of commercial devices (bed-side Hewlett Packard and Finapres-Omedha monitors, respectively). All signals were fed into a personal computer which, following analogic-digital conversion, measured the RR intervals and the systolic arterial pressure at each cardiac cycle. These data were stored for subsequent analysis. After a 30-min period of rest necessary for stabilization, recording of the basal blood pressure and heart rate began. A bolus dose of phenylephrine (2 μg/kg) was then administered intravenously. If an increase in systolic arterial pressure of 15-40 mmHg was not achieved, additional doses were administered in increments of 25 μg up to a maximum of 3.5 μg/kg. The effective dose was repeated at least 3 times. The BRS was then expressed in ms/mmHg as the slope of the regression line relating the RR interval increments to the systolic arterial pressure increments. In accordance with the literature, only the results confirming an adequate increment in the systolic arterial pressure response to the stimulus, i.e. equal to at least 15 mmHg with drug doses no greater than 3.5 μg/kg, and for which the correlation coefficient between the systolic arterial pressure and the RR interval increases was > 0.80 or was statistically significant with a p value < 0.05 were taken into consideration.

Statistical analysis. Data are expressed as mean ± SD. Single regression analysis was performed to evaluate the correlation between variables. The Mann-Whitney U test was performed to analyze differences between groups. Finally, a stepwise logistic regression analysis was carried out to test the incremental predictive value of echo-Doppler and clinical (NYHA class) variables with respect to the BRS value. An alpha error ≤ 5% was considered significant.

Results

At the time of the study 151 patients were in NYHA classes I and II (80%), and 38 patients (20%) in NYHA classes III-IV. The mean echocardiographic EF was 25 ± 7% (range 39-13%). A weak, although highly significant, correlation was found between the BRS and the EF ($r = 0.40$, $p < 0.00001$), age ($r = 0.33$, $p = 0.00001$), NYHA class ($r = 0.34$, $p < 0.00001$), mitral regurgitation ($r = 0.35$, $p < 0.00001$) and deceleration time ($r = 0.20$, $p = 0.006$) (Table I). Patients were then divided into two groups according to a deceleration time value < 140 ms (n = 76, group 1) or ≥ 140 ms (n = 113, group 2). The clinical and echocardiographic data of the two groups are reported in table II. Patients in group 1 had a significantly lower BRS (3 ± 4 vs 6 ± 4 ms/mmHg, $p < 0.00001$), a lower EF (20 ± 6 vs 28 ± 7%, $p < 0.00001$), more severe left ventricular enlargement (end-diastolic volume index 137 ± 43 vs 113 ± 45 ml/m^2, $p < 0.00001$) and left atrial dilation (25 ± 6 vs 20 ± 5 cm^2, $p < 0.00001$), more severe mitral regurgitation (3 ± 1 vs

Table I. Correlations between baroreflex sensitivity, Doppler echocardiographic data and clinical status.

	Age	NYHA class	EDVi	EF	E/A	DT	LA	MR
BRS	-0.33	-0.34	-0.27	0.40	-0.15	0.20	-0.28	-0.35
p	0.00001	< 0.00001	0.0001	< 0.00001	0.03	0.006	0.00001	< 0.00001

BRS = baroreflex sensitivity; DT = deceleration time; EDVi = end-diastolic volume index; EF = ejection fraction; LA = left atrium; MR = mitral regurgitation.

Table II. Clinical and echocardiographic data of patients with restrictive vs non-restrictive left ventricular filling pattern.

	Group 1 (n=76)	Group 2 (n=113)	p
Age (years)	55 ± 9	56 ± 10	NS
EF (%)	20 ± 6	28 ± 7	< 0.00001
EDVi (ml/m^2)	137 ± 43	113 ± 45	< 0.00001
E wave (cm/s)	96 ± 26	64 ± 24	< 0.00001
A wave (cm/s)	46 ± 27	71 ± 22	< 0.00001
E/A	2.4 ± 1	1.4 ± 1	0.0001
LA (cm^2)	25 ± 6	20 ± 5	< 0.00001
MR	3 ± 1	2.3 ± 1	< 0.00001
BRS (ms/mmHg)	3 ± 4	6 ± 4	< 0.00001
NYHA class	2.3 ± 0.6	1.8 ± 0.5	< 0.00001
Diuretics (n=)	81	86	NS
Digoxin (n=)	78	70	NS
ACE-inhibitors (n=)	81	104	NS
Beta-blockers (n=)	11	16	NS

Abbreviations as in table I.

Table III. Predictors of depressed baroreflex sensitivity at stepwise logistic regression analysis.

	χ^2	p	OR	Range
DT	35	0.0001	5.53	2.4-12.9
MR	17	0.0001	4.03	1.76-9.21
Age	15	0.0001	4.85	2.06-11.4
NYHA class	12	0.0001	6.43	2.08-19.8

OR = odds ratio. Other abbreviations as in table I.

2.3 ± 1, p < 0.00001) and were in a higher NYHA class (2.3 ± 0.6 vs 1.8 ± 0.5, p < 0.00001). Medications at the time of the study were similar in the two groups.

On the basis of the results of the ATRAMI study[4], we decided to consider BRS responses ≥ 3 ms/mmHg as normal or only mildly depressed, and those < 3 ms/mmHg as markedly depressed. At multivariate stepwise logistic regression analysis, the following variables were found to be predictors of a depressed BRS: deceleration time, mitral regurgitation, age and NYHA class (Table III).

Discussion

Profound abnormalities in the neurohumoral control of the circulatory system occur in congestive heart failure and the severity of the functional autonomic impairment seems to correlate with the reduction in cardiac reserve[5-7]. Proposed reflex mechanisms for generalized neurohumoral activation include decreased input from inhibitory baroreceptor afferent vessels and increased input from excitatory afferent vessels arising from arterial chemoreceptors and skeletal or lung metaboreceptors. Arterial baroreflex control of heart rate has been found to be abnormal both in humans with heart failure[8-10] and in a variety of experimental models of congestive heart failure. The mechanisms responsible for the autonomic dysfunction associated with congestive heart failure are not fully understood. Blunting of baroreflexes may be due to structural or functional derangement in the afferent and efferent limbs of the reflex arc. Besides, alterations of the mechanical properties of the arterial wall at the baroreceptor site may be due to circulatory congestion and increased vascular sodium content[11].

Impaired parasympathetic control of the heart rate may precede sympathetic activation, as reported in patients with idiopathic dilated cardiomyopathy[6]. The parasympathetic control of the heart rate may be assessed by quantifying the reflex bradycardic response to the pressor stimulus by the pure alpha$_1$ receptor agonist phenylephrine (BRS), or by analysis of heart rate variability in the time and frequency domains (vagal tone). Both BRS and heart rate variability appear to be independent risk factors for mortality after myocardial infarction[4,12]; more recently, some new data have been reported on the prognostic importance of BRS impairment in heart failure patients[13]. We tried to gain further insight into the pathophysiology of defective parasympathetic control of heart rate in congestive heart failure, and in the present study we addressed the correlation between BRS (as an index of parasympathetic withdrawal), left ventricular performance and functional status.

A strong correlation between the deceleration time of left ventricular early filling and pulmonary wedge pressure has recently been demonstrated in patients with left ventricular systolic dysfunction and chronic heart failure[3]. The original hypothesis of our study was that those patients with a moderate to severe reduction in left ventricular function (EF < 40%) and with diastolic dysfunction, represented by a short deceleration time of early filling as an index of a restrictive diastolic filling pattern, should have a more compromised hemodynamic situation, and, as a consequence, a more evi-

dent autonomic derangement. Preliminary data seemed to confirm our hypothesis[14] thus encouraging us to study a wider population. In the present study we were able to find only a poor (even if highly significant) correlation between BRS values and echocardiographic indexes of both systolic and diastolic left ventricular function (Table I). In particular, the low correlation between the deceleration time, as an index of a restrictive filling pattern and then of an elevated left ventricular filling pressure, and BRS ($r = 0.20$) was similar to that recently reported by Mortara et al.[13] between pulmonary wedge pressure and BRS ($r = -0.29$); a multifactorial origin of baroreflex depression has been hypothesized to explain this lack of correlation. When we divided patients into two groups according to the deceleration time values < 140 and ≥ 140 ms, strong and highly significant differences between the two groups were found in terms of left ventricular volume, EF, mitral regurgitation, left atrial enlargement, BRS, NYHA functional class, and age. Finally, at multivariate regression analysis, the deceleration time emerged as the best predictor of a depressed BRS, followed by mitral regurgitation, age, and NYHA functional class. This finding confirms that, in patients with heart failure, the presence of a short deceleration time of early transmitral flow by Doppler echocardiography is not only an accurate indicator of elevated left ventricular filling pressures[3] but also a powerful predictor of a more advanced autonomic derangement in terms of a depressed BRS. In our heart failure patients, the second predictive variable of low BRS was the degree of mitral regurgitation. This was not surprising: more severe mitral regurgitation can be found either if the systemic blood pressure cannot be fully justified by the extremely poor left ventricular performance or when ventricular dilation is so pronounced that the mitral valve apparatus is completely deranged and consequently massively incontinent. These are typical situations in severe heart failure, in which neuroendocrine activation is definitively established and extremely difficult to counteract. Age emerged as the third predictor of a depressed BRS: older patients more frequently show both left ventricular diastolic dysfunction and subclinical alterations of BRS. The significance of the latter is uncertain. This may contribute to explain the importance of age as an independent predictor of an abnormal BRS. Finally, the fourth predictor of a depressed BRS was the NYHA class: to date there are few data suggesting any correlation between the functional status and a depressed BRS[13]. On the contrary, the Doppler transmitral flow pattern has been reported to be significantly related to the NYHA class[15] and the occurrence of symptoms during exertion: according to data reported by Xie et al.[16], the restrictive pattern emerges as an independent determinant of an advanced NYHA class in patients with mild to moderate congestive heart failure. Left ventricular volumes and EFs were not found to be independently related to BRS. This indicates that, in patients with similar degrees of left ventricular systolic dysfunction, the presence of a short deceleration time at echo-Doppler as an index of a restrictive diastolic filling pattern and thus of a more severe hemodynamic deterioration (elevated pulmonary wedge pressure), predicts a depressed BRS.

In conclusion, patients with chronic heart failure often show some degree of autonomic dysfunction that can be easily detectable by assessing the BRS (phenylephrine test). On the other hand, echo-Doppler evaluation allows a non-invasive estimate of left ventricular diastolic filling and a reliable prediction of hemodynamic variables such as the pulmonary wedge pressure. This study clearly demonstrates that a restrictive left ventricular filling pattern, as expressed by a short deceleration time of the E wave at transmitral Doppler echocardiography, is highly predictive of autonomic dysfunction as expressed by a low BRS. The degree of mitral regurgitation, age and NYHA functional class are also predictive of a depressed BRS.

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