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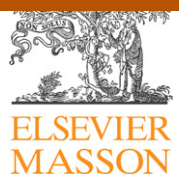

CLINICAL RESEARCH

Predictors of B-type natriuretic peptide and left atrial volume index in patients with preserved left ventricular systolic function: An echocardiographic-catheterization study

Facteurs prédictifs du BNP et du volume de l'oreillette gauche chez les patients avec fonction systolique ventriculaire gauche préservée : une étude par échocardiographie Doppler et cathétérisme

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KEYWORDS
Natriuretic peptide;
Brain;
Left atrium;
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Confounding factors

Summary
Background. — B-type natriuretic peptide (BNP) and left atrial volume index (LAVi) are used as surrogate measures for global myocardial function and are recommended for the diagnosis of heart failure with normal ejection fraction. Little is known, however, about predictors in patients with preserved systolic function.
Aims. — To identify factors that influence the relation of BNP and left atrial size to invasively determined left ventricular end-diastolic pressure in stable patients with preserved left ventricular systolic function.
Methods. — Fifty-nine consecutive patients were included prospectively. Clinical, biological, Doppler echocardiographic and invasive variables were collected simultaneously.
Results. — BNP was predicted independently by left ventricular ejection fraction, diastolic function and age ($p < 0.05$). LAVi was predicted independently by left ventricular mass index and invasive left ventricular end-diastolic pressure ($p < 0.01$). BNP predicted increased left ventricular end-diastolic pressure greater than 16 mmHg ($p = 0.004$); the optimal cut-off value

Abbreviations: AUC, Area under the receiver-operating characteristic curve; BNP, B-type natriuretic peptide; HFnlEF, Heart failure with normal ejection fraction; LAVi, Left atrial volume index.

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was 33 pg/mL (area under the receiver-operating characteristic curve [AUC] 0.74 [0.6—0.84], $p < 0.001$, sensitivity 72%, specificity 70%). LAVi predicted increased left ventricular end-diastolic pressure ($p < 0.001$); the optimal cut-off value for LAVi was 26 mL/m^2 (AUC 0.87 [0.75—0.94], $p < 0.001$; sensitivity 85%, specificity 80%). Unlike BNP ($p = 0.1$), LAVi performed well in patients with abnormal relaxation at mitral filling ($p < 0.01$).
Conclusion. — BNP is influenced by age in stable patients with preserved systolic function and should be interpreted cautiously. LAVi is a powerful surrogate for invasively determined left ventricular end-diastolic pressure regardless of age and mitral filling.

MOTS CLÉS
Peptide natriurétique de type B ;
Oreillette gauche ;
Cathétérisme ;
Facteurs prédictifs

Résumé
Contexte. — Le peptide natriurétique de type B (BNP) et le volume de l'oreillette gauche reflètent la fonction myocardique globale et sont recommandés dans le diagnostic de l'insuffisance cardiaque diastolique, mais leurs facteurs prédictifs sont peu connus en cas de fonction systolique préservée.
Objectifs. — Identifier les facteurs influençant la corrélation de ces deux paramètres avec la pression télédiastolique ventriculaire gauche chez les patients stables avec fonction systolique préservée.
Méthodes. — Cinquante-neuf patients consécutifs ont été inclus de manière prospective. Plusieurs données cliniques, biologiques, échographiques et invasives ont été collectées simultanément.
Résultats. — Le BNP était indépendamment prédit par la fraction d'éjection, la fonction diastolique et l'âge ($p < 0,05$). Le volume de l'oreillette gauche était indépendamment prédit par la masse ventriculaire et la pression télédiastolique ventriculaire gauche invasive ($p < 0,01$). Le BNP prédisait une élévation de la pression télédiastolique ventriculaire gauche supérieure à 16 mmHg ($p = 0,004$) ; la valeur seuil optimale était 33 pg/mL (aire sous la courbe ROC de 0,74 [0,6—0,84], $p < 0,001$, sensibilité 72 %, spécificité 70 %). L'oreillette gauche prédisait une élévation de la pression télédiastolique ventriculaire gauche ($p < 0,001$) ; la valeur seuil optimale était 26 mL/m^2 (aire sous la courbe ROC de 0,87 [0,75—0,94], $p < 0,001$, sensibilité 85 %, spécificité 80 %). À la différence du BNP ($p = 0,1$), l'oreillette gauche restait prédictive chez les patients avec anomalie de relaxation au flux Doppler mitral ($p < 0,01$).
Conclusion. — La concentration en BNP est influencée par l'âge chez les patients stables avec fonction systolique préservée et doit être interprétée avec prudence. Le volume de l'oreillette gauche est un puissant prédicteur de la pression télédiastolique ventriculaire gauche invasive indépendamment de l'âge et du profil mitral.

Background

HFnlEF accounts for half of patients with the clinical syndrome of heart failure. Establishing this medical condition is difficult in daily clinical practice, although specific recommendations have been proposed recently by French and European cardiology societies [1,2]. In particular, affirmation of HFnlEF is challenging in stable patients because exertional symptoms are non-specific for the diagnosis [3,4]. Natriuretic peptides and left atrial size have been related successfully to invasively determined left ventricular end-diastolic pressure —a well-recognized marker of global myocardial dysfunction— and have been proposed subsequently for the diagnosis of HFnlEF in patients with normal ejection fraction [1,2]. However, these two variables are likely to be influenced by several confounders and little is known about factors affecting natriuretic peptides and left atrial size in stable patients with preserved left ventricular systolic function [5—7]. The aim of the present study was to identify factors that influence the relation of BNP and left atrial size to invasively determined left ventricular end-diastolic pressure in stable patients with preserved left ventricular systolic function.

Methods

Patients

Seventy-eight consecutive patients referred for clinically indicated catheterization were enrolled prospectively after written informed consent was obtained. Patients had to be in sinus rhythm, clinically stable and free of symptoms and signs of decompensated heart failure and symptomatic coronary artery disease (including angina, acute coronary syndromes and acute myocardial infarction) to be enrolled. All data (laboratory tests, Doppler echocardiography and catheterization) were collected on the same morning for each patient. Patients with a left ventricular ejection fraction less than 45%, severe left-sided valve disease and/or mild to moderate mitral stenosis at Doppler echocardiography were excluded. The final study group comprised 59 patients.

Laboratory tests

A blood sample was collected from all the patients during bed rest, early in the morning, to avoid the potential influence of circadian variations and exercise on BNP concentration [8,9], which was measured at our institution's laboratory with an ADVIA Centaur system (Siemens Healthcare Diagnostics Inc., Tarrytown, NY, USA; range of 5—5000 pg/mL). ADVIA Centaur BNP is harmonized to the Biosite Triage assay with similar decision threshold values. Serum creatinine and serum haemoglobin were measured at the same time. Creatinine clearance (mL/min/m^2) was calculated with the Cockroft formula.

Doppler echocardiography

All patients underwent bedside Doppler echocardiography with an Acuson Sequoia ultrasound system (Siemens, Mountain View, CA, USA). All echocardiography measurements were made by the same operator, who was blinded to the data; the measurements were performed according to recommendations from the American Society of Echocardiography [10] and validated by a second experienced operator. Optimal Doppler gain and filter settings were adjusted carefully. Three to five beats were averaged for all variables. Fractional shortening was measured in all patients. Left ventricular ejection fraction was measured with Simpson's biplane method; Teichholz's method was used in association with a visual estimate in patients with inadequate two-dimensional images in apical views. Peak early and late diastolic mitral velocities (E and A, cm/s) were recorded placing the pulsed-wave Doppler sample volume between the tips of mitral leaflets. Diastolic function was categorized according to mitral filling pattern and invasive data as follows: normal mitral filling (E/A ratio 1—2 and normal left ventricular end-diastolic pressure); abnormal relaxation (E/A ratio < 1); pseudonormal mitral filling (E/A ratio 1—2 and increased left ventricular end-diastolic pressure); and restrictive mitral filling (E/A ratio > 2 and increased left ventricular end-diastolic pressure). The severity of mitral regurgitation was assessed by the flow convergence method. The tissue Doppler-derived peak systolic s' velocity was measured by spectral tissue Doppler at the lateral side of the mitral annulus and used as a surrogate for longitudinal systolic function. The peak early diastolic e' velocity was measured by spectral tissue Doppler at the lateral side of the mitral annulus and used as a surrogate for left ventricular relaxation. The E/e' ratio was calculated and used as a non-invasive surrogate for instantaneous left atrial pressure. Maximal left atrial volume was measured at end-systole in the four-chamber apical view by Simpson's method and indexed to the body surface area (LAVi, mL/m^2) [11].

Invasive data

Baseline systolic aortic pressure and left ventricular end-diastolic pressure were derived from left-sided heart catheterization with a 4—6F fluid-filled pigtail catheter. Five consecutive beats were averaged at the end of expiration. The presence of coronary artery disease at coronary angiography was defined as a stenosis greater than 70% in one or more epicardial arteries, detected by two experienced operators. Increased left ventricular end-diastolic pressure was defined by a value greater than 16 mmHg in this setting [2].

Statistical analysis

Descriptive data are given as means ± standard deviations or medians [25th—75th percentiles] when appropriate. Log-transformed data were used for BNP concentrations. Variables of influence were identified by multiple regression analysis. The multivariable model included only variables that reached significance in the univariate model (i.e. $p < 0.05$), using a stepwise approach. The diagnostic performance of BNP, LAVi and E/e' in predicting invasive left ventricular end-diastolic pressure greater than 16 mmHg was assessed by logistic regression analysis. The diagnostic performance of variables was also evaluated using the area under the receiver-operating characteristic curve (AUC), which was provided with its 95% confidence interval. The optimal cut-off corresponded to the value with the greatest accuracy. A p-value less than 0.05 was considered to be statistically significant. Medcalc statistical software (version 11.1.0, MedCalc Software, Mariakerke, Belgium) was used for the purpose of statistical analysis.

Results

Baseline clinical characteristics are summarized in Table 1. Age ranged from 34—89 years. Five patients presented with chronic kidney disease defined by a creatinine clearance less than 45 mL/min/m^2. Invasive left ventricular end-diastolic pressure was increased in 39 patients (66%). BNP correlated poorly with LAVi ($r^2 = 0.07$, $p = 0.036$).

Predictors of B-type natriuretic peptide concentration

By univariate analysis, BNP was predicted by age ($p < 0.001$), systolic blood pressure ($p = 0.01$), left ventricular ejection fraction (inverse relation, $p < 0.001$), s' (inverse relation, $p = 0.01$), E/e' ($p < 0.001$), left ventricular mass index ($p = 0.001$), mitral regurgitation ($p < 0.001$), indexed left ventricular end-diastolic diameter ($p = 0.003$), diastolic function ($p = 0.004$), invasive left ventricular end-diastolic pressure ($p < 0.001$), creatinine clearance (inverse relation, $p = 0.005$), serum haemoglobin (inverse relation, $p = 0.001$) and diuretic therapy ($p = 0.03$), but not by sex, body mass index, heart rate, fractional shortening, e' or the extent of coronary artery disease (Table 2).

By multivariable analysis, left ventricular ejection fraction (inverse relation, $p < 0.001$), age ($p = 0.003$) and diastolic function ($p = 0.01$) independently predicted BNP (Table 2).

Predictors of left atrial volume index

By univariate analysis, LAVi was predicted by age ($p = 0.006$), left ventricular mass index ($p < 0.001$), mitral regurgitation ($p = 0.02$), left ventricular end-diastolic diameter ($p = 0.02$), diastolic function ($p = 0.006$) and invasive left ventricular end-diastolic pressure ($p < 0.001$), but not by sex, systolic

Table 1 Baseline characteristics of the study population ($n = 59$).

Variable	
Age (years)	64 ± 12
Men	37 (63)
Systolic blood pressure (mmHg)	148 ± 31
Heart rate (beats/min)	65 [55—74]
Body mass index (kg/m^2)	27 ± 5
New York Heart Association class	2 ± 0.7
Left ventricular ejection fraction (%)	59 ± 7
Fractional shortening (%)	34 ± 6
Tissue Doppler s' velocity (cm/s)	9.4 [8—10]
Tissue Doppler e' velocity (cm/s)	10.5 [9.4—12.5]
Tissue Doppler E/e' ratio	6.6 [5.2—8.8]
Diastolic function	
Normal	7 (12)
Impaired relaxation	28 (47)
Pseudonormal	21 (36)
Restrictive	3 (5)
Left ventricular mass index (g/m^2)	92 [80—109]
Indexed left ventricular end-diastolic diameter (mm/m^2)	27 ± 3.5
Left atrial volume index (mL/m^2)	31 [22—39]
B-type natriuretic peptide concentration (pg/mL)	53 [20—137]
Medical history	
Coronary artery disease	29 (49)
Hypertension	34 (58)
Diabetes mellitus	21 (36)
Dyslipidaemia	32 (54)
Pulmonary oedema	5 (9)
Chronic pulmonary disease	9 (15)
Chronic medication	
Diuretic	20 (34)
Beta-blocker	35 (59)
ACE inhibitor/ARB	40 (68)
Invasive left ventricular end-diastolic pressure (mm Hg)	20 ± 7
Coronary artery disease	30 (51)
One vessel	11 (19)
Two vessels	8 (14)
Three vessels	11 (19)
Serum haemoglobin (g/dL)	12.8 ± 1.7
Creatinine clearance (mL/min)	85 [68—108]

Data are means ± standard deviations, medians [25th—75th percentiles] or numbers (%).
ACE: angiotensin-converting enzyme; ARB: angiotensin-receptor blocker.

blood pressure, heart rate, body mass index, left ventricular ejection fraction, s', e', E/e', fractional shortening, the extent of coronary artery disease, creatinine clearance, serum haemoglobin or treatment (Table 2).

By multivariable analysis, invasive left ventricular end-diastolic pressure ($p = 0.001$) and left ventricular mass index ($p = 0.005$) independently predicted LAVi (Table 2).

Diagnostic accuracy of B-type natriuretic peptide and left atrial volume index in predicting increased left ventricular end-diastolic pressure

The E/e' ratio predicted increased left ventricular end-diastolic pressure (odds ratio 1.4 [1.07—1.9], $p = 0.01$). The optimal cut-off value for E/e' was 6.7 (AUC 0.69 [0.56—0.80], $p < 0.01$, sensitivity 56%, specificity 80%). Log (BNP) correlated well with left ventricular end-diastolic pressure ($r = 0.50$ [0.28—0.67], $p < 0.001$) (Fig. 1). BNP was a good predictor of increased left ventricular end-diastolic pressure (odds ratio 5.0 [1.7—15.0], $p = 0.004$). The optimal cut-off value was 33 pg/mL (AUC 0.74 [0.6—0.84], $p < 0.001$, sensitivity 72%, specificity 70%). The cut-off value of 100 pg/mL was 46% sensitive and 80% specific. LAVi correlated well with left ventricular end-diastolic pressure ($r = 0.48$ [0.25—0.65], $p < 0.001$) (Fig. 2). LAVi was a powerful predictor of increased left ventricular end-diastolic pressure (odds ratio 1.19 [1.09—1.3], $p < 0.001$). The optimal cut-off value for LAVi was 26 mL/m^2 (AUC 0.87 [0.75—0.94], $p < 0.001$; sensitivity 85%, specificity 80%).

Table 2 Multiple regression analysis of factors affecting B-type natriuretic peptide and left atrial volume index.

Variable	B-type natriuretic peptide		Left atrial volume index	
	Univariate analysis *p*-value	Multivariable analysis *p*-value	Univariate analysis *p*-value	Multivariable analysis *p*-value
Age	< 0.001	0.003	0.006	NS
Sex	0.07	-	0.22	-
Body mass index	0.52	-	0.06	-
Systolic blood pressure	0.01	NS	0.21	-
Heart rate	0.78	-	0.33	-
Left ventricular ejection fraction	< 0.001	< 0.001	0.1	-
Tissue Doppler s' velocity	0.01	NS	0.19	-
Tissue Doppler e' velocity	0.09	-	0.34	-
Tissue Doppler E/e' ratio	< 0.001	NS	0.07	-
Fractional shortening	0.62	-	0.7	-
Left ventricular mass index	0.001	NS	< 0.001	0.005
Indexed left ventricular diastolic diameter	0.003	NS	0.02	NS
Mitral regurgitation	< 0.001	NS	0.02	NS
Diastolic function	0.004	0.01	0.006	NS
Invasive left ventricular end-diastolic pressure	< 0.001	NS	< 0.001	0.001
Extent of coronary artery disease	0.09	-	0.58	-
Diuretics	0.03	NS	0.08	-
Beta-blockers	0.23	-	0.19	-
ACE inhibitor/ARB	0.2	-	0.52	-
Creatinine clearance	0.005	NS	0.67	-
Serum haemoglobin	0.001	NS	0.33	-

ACE: angiotensin-converting enzyme; ARB: angiotensin receptor blocker; NS: not significant ($p > 0.05$); -: not entered into the multivariable model.

Comparison of ROC curves showed that LAVi performed better than E/e' ($p = 0.015$) and that BNP performed as well as E/e' ($p = 0.5$). The difference between BNP and LAVi did not reach statistical significance ($p = 0.06$).

Diagnostic accuracy of B-type natriuretic peptide and left atrial volume index in predicting increased left ventricular end-diastolic pressure in patients with abnormal relaxation

Twenty-eight patients presented with abnormal relaxation at mitral filling pattern, of whom 15 had increased left ventricular end-diastolic pressure.

Unlike E/e' ($p = 0.1$) and BNP ($p = 0.1$), LAVi was predictive of increased left ventricular end-diastolic pressure (odds ratio 1.2 [1.05—1.4], $p = 0.007$). The optimal cut-off value for LAVi was 24 mL/m^2 (AUC 0.91 [0.74——0.98], $p < 0.001$; sensitivity 93%, specificity 85%).

Discussion

To our knowledge, this is the first study to compare predictors of BNP and LAVi, two well-recognized markers of cardiac dysfunction, in a population of patients with preserved systolic function and invasive data. As expected, BNP and LAVi were not impacted similarly, which accounts for the poor correlation that has been observed between these two variables.

Along with invasively determined left ventricular end-diastolic pressure, several factors have been identified that influence natriuretic peptide concentrations [12—19]: age, body mass index, left ventricular systolic function, diastolic wall stress, renal function and serum haemoglobin. Our data suggest that, along with systolic and diastolic function, ageing impacts on BNP concentration significantly and independently in stable patients with preserved systolic function. This suggests that this clinical variable should be taken into consideration before interpreting BNP

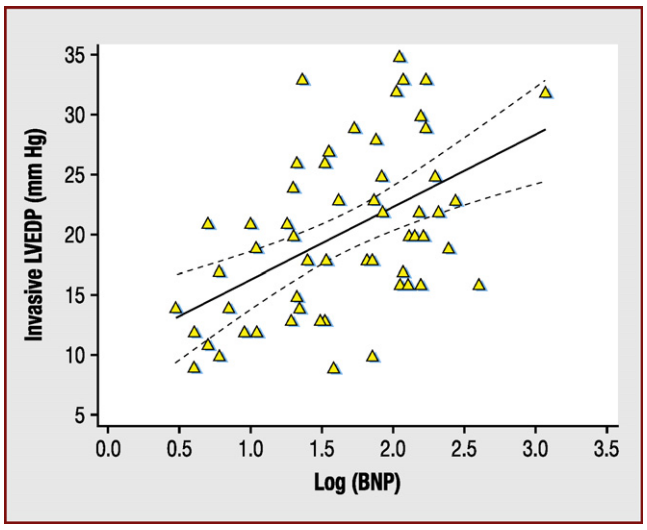

Figure 1. Scatterplot of the relationship between log-transformed data for B-type natriuretic peptide (log [BNP]) and invasively measured left ventricular end-diastolic pressure (LVEDP). The correlation coefficient was 0.50 [0.28—0.67] ($p < 0.001$). The solid line corresponds to the regression line (LVEDP = 6.1 × log [BNP] + 10.2) and the dotted lines correspond to its 95% confidence interval.

concentration in this setting [20] and that further studies are necessary to delineate the diagnostic relevance of natriuretic peptides in specific age groups. Furthermore, in the present study, in a large proportion (90%) of patients with invasive left ventricular end-diastolic pressure greater than 16 mmHg, BNP concentrations were lower than the standard threshold value of 200 pg/mL proposed currently in European recommendations [2]. This observation is consistent with studies published previously, which reported unexpectedly low BNP concentrations (< 100—200 pg/mL) in stable patients with HFnlEF [21,22]. However, there was

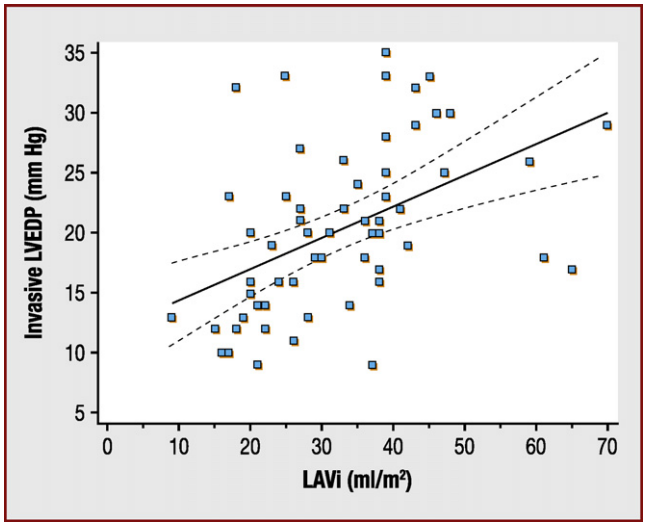

Figure 2. Scatterplot of the relationship between left atrial volume index (LAVi) and invasively measured left ventricular end-diastolic pressure (LVEDP). The correlation coefficient was 0.48 [0.25—0.65] ($p < 0.001$). The solid line corresponds to the regression line (LVEDP = 0.26 × LAVi + 11.8) and the dotted lines correspond to its 95% confidence interval.

no invasive evidence of this medical condition in any of these studies. Our results highlight in patients with invasive haemodynamics that threshold values for the diagnosis of HFnlEF should be established according to clinical presentation (i.e. stable vs decompensated state) [2,7].

In the present study, LAVi reflected invasively determined left ventricular end-diastolic pressure strongly and independently in stable patients with preserved left ventricular systolic function. This finding confirms those of studies published previously, which included predominantly patients with depressed left ventricular systolic function [23,24]. Left ventricular hypertrophy *per se* impacts on left atrial size, which may explain in part the poor correlation between left atrial volume and left ventricular diastolic pressures in hypertrophic cardiomyopathy [25]. Increased left ventricular end-diastolic pressure at rest is a landmark of severe left ventricular dysfunction, and subsequently of HFnlEF in symptomatic patients with preserved systolic function [2]. Previous studies have established the value of left atrial size for the prediction of prevalent [26—28] and incident [29,30] HFnlEF; however, invasive haemodynamics were not available in any of these works. As a straightforward consequence of current literature and the present study, LAVi can be used safely as part of a multiparametric approach for the diagnosis of HFnlEF in stable patients, regardless of age and mitral filling [2].

Study limitations

There are some limitations in the present study. The number of patients is relatively small, although statistically significant results have been achieved. However, patients with symptomatic coronary artery disease were not included in the study group because active ischaemia is likely to impact on BNP concentration. Simpson's biplane method was not used for assessing left atrial volume because the anterior wall of the left atrium is sometimes difficult to delineate clearly. Furthermore, it has been established that the single plane method is clinically relevant for daily practice [11].

Conclusion

BNP and LAVi, which are synonymous with 'glycosylated haemoglobin' in terms of global myocardial function, are not affected similarly in stable patients with preserved left ventricular systolic function. While BNP is influenced by age, LAVi is a robust surrogate for invasively determined left ventricular end-diastolic pressure, regardless of age and mitral filling. Therefore, LAVi can be used safely for the diagnosis of HFnlEF in stable patients.

Conflict of interest statement

None.

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