

The role of B-type natriuretic peptide in the evaluation of left atrioventricular valve regurgitation following surgical repair of partial atrioventricular canal

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Abstract

Background: Left atrioventricular valve (LAVV) regurgitation usually follows surgical repair of partial atrioventricular canal (PAVC). Although measurements of B-type natriuretic peptide (BNP) levels are useful for the monitoring and prediction of outcomes in chronic mitral regurgitation, no data are available on the role of BNP measurements in the assessment of LAVV regurgitation in patients after surgical correction of PAVC.

Aim: To determine the role of plasma BNP determination in the assessment of LAVV regurgitation in patients after surgical repair of PAVC.

Methods: We evaluated 41 patients who had undergone surgery for PAVC between 1968 and 2005 with preserved left ventricular ejection fraction (LVEF, mean age at follow-up: 39.2 ± 14.0 years, mean age at the time of surgery: 31.3 ± 15.6 years, 32 females) and 13 healthy controls (mean age: 38.9 ± 13.2 years, 9 females). All the subjects had undergone transthoracic echocardiography and had their plasma BNP levels determined. LAVV regurgitation was assessed qualitatively on 1+ to 4+ grading scale and quantitatively by calculating the effective regurgitant orifice area (EROA).

Results: LAVV regurgitation was present in 40 (97.6%) patients. Compared to patients with mild-to-moderate LAVV regurgitation (grade 1+ to 2+/EROA < 0.4 cm²) evaluated qualitatively and quantitatively, the group with severe regurgitation (grade 3+ to 4+/EROA ≥ 0.4 cm²) had higher values of left atrial volume (LAVol) and right ventricular (RV) systolic pressure, although there was no significant difference in plasma BNP levels. There were significant correlations between BNP levels and LAVol ($r = 0.54$, $p = 0.0001$), age at follow-up ($r = 0.61$, $p = 0.0001$), age at the time of surgery ($r = 0.58$, $p = 0.0001$), RV diastolic diameter ($r = 0.38$, $p = 0.02$) and RV systolic pressure ($r = 0.48$, $p = 0.002$). Multivariate logistic regression analysis showed that only LAVol and age at the time of surgery but not the degree of LAVV regurgitation were independently associated with elevated plasma BNP levels.

Conclusions: In patients late after surgical repair of the PAVC with preserved LVEF, plasma BNP levels reflect the consequences of the shunt at atrial level and LAVV regurgitation expressed by LAVol but it does not allow to estimate the severity of regurgitation.

Key words: partial atrioventricular canal, B-type natriuretic peptide

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INTRODUCTION

Partial atrioventricular canal (PAVC), also referred to as the ostium primum atrial septal defect (ASD I), is a congenital heart anomaly that accounts for about 15–20% of ASD cases [1, 2]. Abnormal development of the endocardial cushions leads to the formation of a defect affecting the posteroinferior part of the interatrial septum, whose lower margin is formed by atrioventricular valve rings positioned at the same level. An integral element of the condition is the presence of a cleft in the anterior cusp of the left atrioventricular valve (LAVV) causing mitral regurgitation of various severity [3]. Surgical repair is the only treatment option and involves patch closure of the defect, which in most cases is accompanied by simultaneous LAVV valvuloplasty [1, 2, 4–7]. Indications for surgery include haemodynamically significant left-to-right shunting and, additionally, severe LAVV regurgitation [8, 9]. In the long term, the main problem in patient who have undergone surgery is LAVV regurgitation of various severity, which requires repair in 6–18% of the cases [1, 4, 10–15]. Echocardiography is the fundamental assessment method in patients following repair [2].

Determination of B-type natriuretic peptide (BNP) has been found useful for the monitoring and prediction of outcomes in patients with chronic mitral regurgitation [16–24]. There are few reports on using BNP determination in the diagnostic evaluation of patients who have undergone surgery for congenital heart disease, e.g. tetralogy of Fallot [25], or patients with systemic right ventricles (RV) [26, 27]. As there have been no reports in the literature on the usefulness of BNP determination in patients who have undergone surgery for PAVC, the aim of our study was to evaluate the usefulness of BNP determination in the assessment of LAVV regurgitation in this patient group.

METHODS

We evaluated 41 patients registered with the Congenital Heart Disease Outpatient Clinic at the Institute of Cardiology who had undergone surgery for PAVC between 1968 and 2005 and 13 control individuals. The study had been approved by the Field Bioethics Committee. Each patient provided a written informed consent. Patients who met the following criteria were included: a history of primary repair of PAVC, at least 3 months since the surgery, preserved left ventricular ejection fraction (LVEF \geq 55%). The LVEF threshold we adopted excluded patients with left ventricular systolic dysfunction as the cause of elevated BNP. Patients meeting the following criteria were excluded from the study: significant aortic or pulmonary valve disease, a history of implantation of an artificial mitral valve, chronic obstructive pulmonary disease, clinically or angiographically confirmed ischaemic heart disease, renal failure with serum creatinine level \geq 2 mg/dL and lack of patient consent to participate in the study.

In addition to the history and physical examination, the study assessments also included transthoracic echocardiography and determination of serum BNP. Echocardiography was performed using Vivid 7 from GE Medical System and a 2.5-MHz transducer, with the patient in the left lateral position during held end-expiration. The data were archived on VHS tapes. The protocol included M-mode, 2D, continuous- and pulse-wave Doppler and colour Doppler imaging. For the purposes of further analysis we assessed the following parameters: left ventricular systolic dimension (LVSD), left ventricular diastolic dimension (LVDD), left atrial volume (LAVol) calculated with the ellipsoid method, right ventricular diastolic dimension (RVDD) in the parasternal long axis view, LVEF by the Simpson method in 2D images, and right ventricular systolic pressure (RVSP) from tricuspid regurgitant jet velocity. LAVV regurgitation was evaluated qualitatively by determining the regurgitant jet range on Sellers' 1+ to 4+ grading scale [28, 29] and quantitatively by calculating the effective regurgitant orifice area (EROA). All the measurements were performed in accordance with the AHA/EAE recommendations [30].

Serum BNP levels were determined by immunoradiometric assay (IRMA (Shinoria BNP, CIS bio international, a subsidiary of Schering S.A., Gif-sur-Yvette à Cadet, France). Plasma was obtained from blood samples collected to cooled EDTA-containing tubes (1.5 ng/mL of blood). Blood was centrifuged immediately after collection at 3000 g and 4°C for 15 min the samples were stored at –70°C until completion of all the determinations.

The distribution of the study variables was evaluated using the Kolmogorov-Smirnov test. Data with a normal distribution were expressed as means \pm SD and those whose distribution was not normal were expressed as medians and ranges. Groups were compared using the χ^2 test and the t-Student test (the Mann-Whitney test for non-normally distributed variables). Correlations between the variables were assessed using Pearson's or Spearman's coefficients of correlation. The relationship between BNP levels and the study parameters were assessed using uni- and multivariate linear and logistic regression. For variables with a non-normal distribution logarithmic values (natural logarithm) were used in correlation and regression analyses. A p values equal to or less than 0.05 were considered statistically significant.

RESULTS

We evaluated 41 patients. The mean age at the time of surgery and at follow-up was 31.3 ± 15.6 (range: 2–62, median: 30) years and 39.2 ± 14.0 (range: 14–66, median: 37) years, respectively. The mean time from surgery was 7.9 ± 7.3 years (range: 3 months to 39 years, median: 8 years). Females predominated (32 [78%]). Most patients (35 [85.4%]) were in NYHA functional class I, while the remaining 6 patients were in NYHA functional class II. The control group consisted of

Table 1. Parameters assessed in the groups of patients with insignificant (grade < 3+) and significant (grade ≥ 3+) LAVV regurgitation. The 1 patient without regurgitation was included in the group of patients with insignificant LAVV regurgitation

Parameter	Grade < 3+ (n = 23)	Grade ≥ 3+ (n = 18)	P	EROA < 0.4 (n = 32)	EROA ≥ 0.4 (n = 9)	P
LVDD [cm]	4.8 ± 0.5	5.1 ± 0.5	0.057	4.8 ± 0.5	5.3 ± 0.1	0.005
EF [%]	64.9 ± 5.8	67.1 ± 6.2	0.27	67.7 ± 6.9	65.5 ± 5.8	0.34
RVDD [cm]	2.5 ± 0.4	2.5 ± 0.5	0.57	2.5 ± 0.4	2.4 ± 0.5	0.4
RVSP [mm Hg]	35.4 ± 7.5	41.4 ± 8.2	0.02	36.0 ± 7.3	42.3 ± 9.2	0.026
LAVol [cm ³]	51.2 ± 20.1	78.0 ± 41.6	0.018	54.8 ± 23.4	94.5 ± 46.8	0.001
BNP [pg/mL]	38.1 ± 38.5	67.7 ± 76.0	0.10#	51.1 ± 39.3	52.9 ± 65.3	0.9#

#The p value calculated with the Mann-Whitney test; EROA — effective regurgitant orifice area; LAVV — left atrioventricular valve; LVDD — left ventricular diastolic dimension; EF — ejection fraction; RVDD — right ventricular diastolic dimension; RVSP — right ventricular systolic pressure; LAVol — left atrial volume; BNP — B-type natriuretic peptide

13 healthy volunteers (9 [69%] females) at the mean age of 38.9 ± 13.2 (range: 19–63, median: 36) years.

LAVV regurgitation was observed in 40 (97.6%) patients. Qualitative assessment of the LAVV regurgitant jet using the 1+ to 4+ scale revealed grade 1+, 2+, 3+ and 4+ regurgitation in 5, 17, 14 and 4 patients, respectively (12.2%, 41.5%, 34.1% and 9.8%, respectively). LAVV regurgitation was not observed in 1 patient only. Three groups of patients were distinguished on the basis of their EROA values: patients with mild (EROA < 0.20 cm²), moderate (EROA 0.20–0.39 cm²) and severe/significant regurgitation (EROA ≥ 0.40 cm²) (18, 13 and 9 patients, respectively; 45.0%, 32.5% and 22.5%, respectively).

For the purposes of further analysis the patients were divided into the group with insignificant regurgitation (patients qualitatively assessed as having grades 1+ or 2+ regurgitation plus the 1 patient without regurgitation [n = 23]) and the group with significant regurgitation (patients qualitatively assessed as having grades 3+ or 4+ regurgitation [n = 18]). Based on the parameters of quantitative assessment of the significance of LAVV regurgitation the patients were divided into the subgroup with mild to moderate regurgitant jet (EROA < 0.4 cm²) (n = 32) and the subgroup with severe regurgitation (EROA ≥ 4.0 cm²) (n = 9). In both methods, the subgroups differed in terms of the following parameters: LAVol, RVSP, and in the qualitative assessment also in terms of LVDD, with no differences in BNP levels (Table 1). However, BNP levels in the study group differed from those in the control group (51.4 ± 59.5 vs 10.3 ± 12.4 pg/mL, p < 0001). We showed moderately positive correlations between BNP levels and LAVol and the age at the time of surgery and the age at follow-up. Weaker correlations were observed for the parameters affected by the pulmonary artery pressure: RVDD and RVSP (Table 2).

In the multivariate linear regression model of factors associated with BNP levels (log values) including: sex, LAVol, LAVV regurgitation grade in the qualitative assessment (IM-

Table 2. Significant correlations between lnBNP for the entire study group and the investigated parameters

Parameter	r	P
Age at the time of surgery	0.58	0.0001
Age at follow-up	0.61	0.0001
LAVol [cm ³]	0.54	0.0001
RVDD [cm]	0.38	0.02
RVSP [mm Hg]	0.48	0.002

lnBNP — natural logarithm of the B-type natriuretic peptide level; LAVol — left atrial volume; RVDD — right ventricular diastolic dimension; RVSP — right ventricular systolic pressure

plus), age at the time of surgery and age at follow-up, significant factors independently associated with BNP levels turned out to be the following: LAVol, age at the time of surgery and sex (Table 3, Fig. 1). In the multivariate logistic regression model of factors associated with elevated BNP levels (above vs below the maximum value for the control group) including: sex, LAVol, significant LAVV regurgitation (IMplus < 3+ vs IMplus ≥ 3+), age at the time of surgery and age at follow-up, significant factors independently associated with BNP levels turned out to be the following: LAVol (odds ratio [OR] 1.042, 95% confidence interval [CI] 1.006–1.080, p = 0.021) and age at the time of surgery (OR 1.082, 95% CI 1.007–1.163, p = 0.031).

DISCUSSION

The prognosis in patients following surgical repair of PAVC is favourable. In the largest observational study of patients who had undergone surgical repair for ASD I covering the period from 1955 to 1995, rates of 5-, 10-, 20- and 40-year survival were 94%, 93%, 87% and 76%, respectively [4]. The main long-term postoperative complication is LAVV regurgitation [1, 4, 6, 13, 31–34], which — depending on the source — was an indication for repeat surgery in 5% to 18% of the patients [1, 10, 13, 34]. Over the years, the presence and signi-

Table 3. Results of uni- and multivariate relationship between BNP (log-transformed value) and selected parameters

Parameter	lnBNP			
	Univariate analysis		Multivariate analysis	
	Regression coefficient	P	Regression coefficient	P
Sex	-0.238	0.055	-0.244	0.05
Age at the time of surgery	0.038	0.0001	0.051	0.0001
Age at follow-up	0.036	0.002	0.074	0.828
Mitral regurgitation grade (qualitative assessment)	0.568	0.0001	0.05	0.973
LAvol [cm ³]	0.022	0.0001	0.039	0.001
RVSP [mm Hg]	0.075	0.0001	0.154	0.370

lnBNP — natural logarithm of the B-type natriuretic peptide level; LAvol — left atrial volume; RVSP — right ventricular systolic pressure

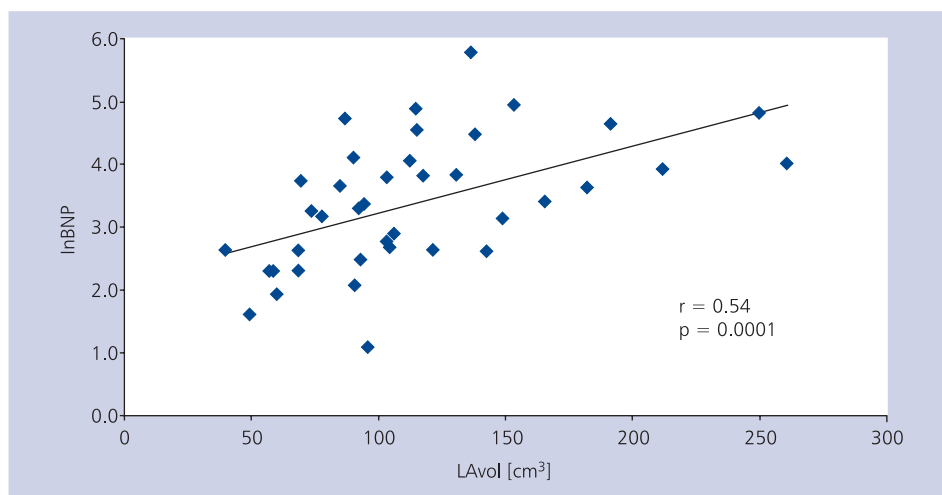


Figure 1. Left atrial size expressed as its volume (LAvol) and the natural logarithm of the B-type natriuretic peptide level (lnBNP). A graph representing the relationship between left atrial size expressed as LAvol in cm³ and the lnBNP

ificance of LAVV regurgitation has been assessed clinically, angiographically and, most recently, echocardiographically. Due to the various assessment methods and their dynamic development, especially the development of echocardiography, it has been difficult to compare the results of various observations. In the study conducted between 1955 and 1995 in a group of 334 patients who had undergone surgery for ASD I (mean age at the time of surgery was 8 years and 23% of the patients were over the age of 20 years), 230 of the patients (69%) had LAVV regurgitation and the regurgitation was considered significant only in 42 of the cases (12.6%) [4]. In a study published in 2009 [13], significant LAVV in the qualitative assessment by Doppler colour was found in a mere 6.7% of the subjects (mean age at the time of surgery was 4.5 years and 9.85 of the patients were over the age of 20 years). However, in a study published in 2010 [31], as many as 31% of the patients 6 months following surgery for PAVC (mean age at the time of surgery: 1.8 years, all the patients

aged below 18 years) had moderate/significant LAVV regurgitation as assessed qualitatively by colour Doppler.

There have been no reports in the literature concerning studies to assess the severity of LAVV regurgitation following ASD I repair using a quantitative method, which is recommended by management standards in acquired valvular heart disease [9]. The difficulties in the assessment of EROA of the LAVV in patients following surgery for PAVC result from its complex mechanism caused by a thickening and deformation of valve leaflets following their repair, incomplete closure of the cleft in the anterior leaflet, changes in the subvalvular apparatus and the frequently observed presence of more than one regurgitant jet [6, 32, 34]. Bearing in mind the above limitations in determining the severity of the regurgitant jet, we employed the quantitative as well as the qualitative method. Comparing the two methods allowed us to distinguish a group of 9 patients requiring particular attention due to severe regurgitation assessed quantitatively.

As a result of the adaptive mechanisms of the cardiovascular system the selection of the optimal timing for surgery in asymptomatic patients with significant mitral regurgitation and preserved LV systolic function is not clearly defined. There are reports that justify early surgical intervention in asymptomatic patients with significant mitral regurgitation if valve repair is possible [35–37]. According to these authors, this approach is justified by better long-term outcomes in patients undergoing surgery. An alternative approach is to qualify patients for surgery when the compensatory mechanisms of volume overload have been exhausted [9, 10]. This is associated with the need for careful monitoring of these patients both for the signs and symptoms and the assessment of LV dysfunction [37].

Many studies have demonstrated the usefulness of determining BNP levels in patients with mitral regurgitation. Detaint et al. [18] showed that BNP levels — irrespective of sex, age, NYHA functional class, significance of mitral regurgitation and LVEF — significantly affected mortality in long-term observation in patients with organic mitral regurgitation. Pizarro et al. [22] adopted a BNP level of ≥ 105 pg/mL as a cut-off point for increased cardiovascular risk in asymptomatic patients with mitral regurgitation and preserved LV systolic function. Sutton et al. [17] demonstrated that only the severity of mitral regurgitation affected serum BNP levels, while other papers show an association of BNP activation with LV and LA enlargement rather than with the severity of regurgitation [18, 19]. In patients with ASD, BNP levels correlated with RV size and RVSP [38]. The association of BNP with sex and age is commonly recognised [39, 40]. In the study group, the correlations of (log-transformed) BNP levels with the study parameters fully correspond to the pathophysiology of BNP secretion (Table 2). We showed moderately positive correlations between BNP levels and LAVol, age at the time of surgery and age at follow-up. We observed weaker correlations between BNP levels and pulmonary artery pressure parameters (RVDD, RVSP). We found no associations between BNP levels and the significance of LAVV regurgitation in the qualitative and quantitative assessments. The use of a more categorical classification according to EROA (patients with EROA < 0.4 cm² and patients with EROA ≥ 0.4 cm²), which allowed us to identify 9 patients with a severe regurgitant jet, also failed to reveal any differences in BNP levels (Table 1). Only LAVol and age at the time of surgery independently affected BNP levels (Table 3). These results are consistent with other authors' findings, who also showed an association of BNP levels with the consequences (LA and LV sizes) rather than with the severity of mitral regurgitation [18, 21]. BNP is therefore a marker of LA remodelling rather than a marker of the severity of mitral regurgitation. Demonstration of this association in our group of patients is of particular importance, as the pathophysiology of BNP secretion may be affected by the consequences of a valvular heart disease with a shunt and by

the irreversible consequences of LAVV regurgitation present before the surgery. Demonstration of an association of LAVol with changes in BNP levels in our study confirms these relationships. To the best of our knowledge, this is the first publication to address BNP levels following surgical treatment of PAVC with LAVV regurgitation. Our results confirm the role of LAVol in the assessment of patients following PAVC repair and this parameter should therefore become an integral element of routine echocardiographic assessment in this patient group.

Limitations of the study

A limitation of our study was the lack of preoperative data, such as LAVol, results of a quantitative assessment of LAVV regurgitation and serum BNP levels, which makes it difficult to analyse the impact of long-term consequences of the condition on BNP levels.

CONCLUSIONS

BNP levels in patients following PAVC repair with preserved LV systolic function reflect the sequelae of a valvular defect with a shunt and the sequelae of LAVV regurgitation (expressed by LAVol) rather than reflecting the severity of the condition.

Conflict of interest: none declared

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Stężenie peptydu natriuretycznego typu B w odległej ocenie niedomykalności lewej zastawki przedsionkowo-komorowej po operacji częściowego kanału przedsionkowo-komorowego

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Streszczenie

Wstęp: Niedomykalność lewej zastawki przedsionkowo-komorowej (LAVV) jest najczęstszym odległym powikłaniem po operacyjnej korekcji częściowego kanału przedsionkowo-komorowego (PAVC). Oznaczanie stężenia peptydu natriuretycznego typu B (BNP) stosuje się w monitorowaniu i ocenie rokowania pacjentów z przewlekłą niedomykalnością mitralną. W piśmiennictwie brakuje danych dotyczących roli oznaczeń BNP w ocenie niedomykalności LAVV u chorych po operacji PAVC.

Cel: Celem pracy było określenie użyteczności oznaczeń stężenia BNP w ocenie niedomykalności LAVV u chorych po operacji PAVC.

Metody: U 41 chorych (wiek w czasie badania $39,2 \pm 14,0$ roku, wiek w czasie operacji $31,3 \pm 15,6$ roku, 32 kobiety) poddanych operacyjnej korekcji PAVC w latach 1968–2005, z zachowaną funkcją skurczową lewej komory oraz u 13 osób z grupy kontrolnej (śr. wiek $38,9 \pm 13,2$ roku, 9 kobiet) wykonano przezklatkowe badanie echokardiograficzne i oznaczono stężenie BNP w surowicy krwi. Niedomykalność LAVV oceniano jakościowo, określając zasięg fali zwrotnej w skali 4-plusowej i ilościowo na podstawie pomiaru efektywnej powierzchni otworu niedomykalności (EROA).

Wyniki: Niedomykalność LAVV stwierdzono u 40 (97,6%) chorych. Wyróżniono podgrupę z nieistotną niedomykalnością ocenianą jakościowo jako 1+ i 2+ i jednego pacjenta bez niedomykalności ($n = 23$) i podgrupę z niedomykalnością istotną ocenianą jako 3+ i 4+ ($n = 18$). Na podstawie parametrów ilościowej oceny istotności niedomykalności LAVV wyodrębniono podgrupę z małą/umiarkowaną falą zwrotną $EROA < 0,4 \text{ cm}^2$ ($n = 32$) oraz ciężką niedomykalnością $EROA \geq 0,4 \text{ cm}^2$ ($n = 9$). W obu metodach podgrupy różniły się objętością lewego przedsionka i skurczowym ciśnieniem w tętnicy płucnej, nie wykazano natomiast różnic w stężeniu BNP. Stężenie BNP w całej grupie badanej różniło się istotnie w porównaniu z grupą kontrolną, odpowiednio $51,4 \pm 59,5$ v. $10,3 \pm 12,4 \text{ pg/ml}$; $p < 0,001$. Wykazano istotne korelacje między stężeniem BNP a objętością lewego przedsionka ($r = 0,54$; $p = 0,0001$), wiekiem w czasie badania ($r = 0,61$; $p = 0,0001$), wiekiem w czasie operacji ($r = 0,58$; $p = 0,0001$), wymiarem rozkurczowym prawej komory ($r = 0,38$; $p = 0,02$) i ciśnieniem skurczowym w prawej komorze ($r = 0,48$; $p = 0,002$). Wieloczynnikowa analiza regresji logistycznej czynników związanych z występowaniem podwyższonego stężenia BNP (powyżej v. poniżej maksymalnej wartości dla grupy kontrolnej) obejmujących płeć, objętość lewego przedsionka, istotną niedomykalność LAVV, wiek w czasie operacji i wiek podczas badania wykazała, że jedynie objętość lewego przedsionka i wiek w czasie operacji, nie zaś stopień niedomykalności LAVV, były niezależnie związane z podwyższonym stężeniem BNP.

Wnioski: Stężenie BNP u pacjentów po operacji częściowego kanału przedsionkowo-komorowego, z zachowaną funkcją skurczową lewej komory odzwierciedla następstwa wady przeciekowej i następstwa niedomykalności LAVV (wyrażone objętością lewego przedsionka), a nie stopień jej nasilenia w ocenie jakościowej i ilościowej.

Słowa kluczowe: częściowy kanał przedsionkowo-komorowy, peptyd natriuretyczny typu B

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