ARTYKUŁ ORYGINALNY / ORIGINAL ARTICLE

B-type natriuretic peptide in patients after percutaneous trans-coronary-sinus mitral annuloplasty

Tomasz Siminiak, Olga Jerzykowska, Michał Kuzemczak, Andrzej Szyszka, Piotr Kalmucki, Artur Baszko

HCP Medical Centre, Poznan University of Medical Sciences, Poznan, Poland

Abstract

Background and aim: Functional mitral regurgitation (MR) remains a significant clinical problem. Surgical valve repair carries a high procedural risk. Thus, percutaneous techniques are under development. One of the most advanced devices for percutaneous mitral annuloplasty (PTMA) is the Carillon™ device. B-type natriuretic peptide (BNP) is a marker of haemodynamic status in heart failure patients. So far, its usefulness in patients after PTMA is unknown.

Methods: Thirteen consecutive patients after successful implantation of the Carillon™ device were enrolled. PTMA was achieved through the coronary sinus in order to improve leaflet coaptation. Before PTMA, immediately after, and at one month follow-up, transthoracic echocardiography was performed. Furthermore, plasma BNP levels, the six-minute walk test (6MWT) and the Naughton treadmill exercise test were evaluated before PTMA and after one month.

Results: In patients after successful PTMA, significant improvement in echocardiographic parameters was maintained at one-month follow-up: vena contracta (0.31 ± 0.03 vs. 0.64 ± 0.03 cm, p < 0.05), effective regurgitant orifice area (0.2 ± 0.02 vs. 0.32 ± 0.05 cm², p < 0.05), MR jet area/left atrial area (32.33 ± 1.98 vs. 47.06 ± 2.3%, p < 0.05) and regurgitant volume (27.84 ± 2.17 vs. 45.25 ± 7.47 mL, p < 0.05). Both the duration of the exercise test (4.3 ± 0.45 vs. 3.12 ± 0.18 min, p < 0.05) and 6MWT (320 ± 29.63 vs. 295.2 ± 13.4 m, p < 0.05) improved. Furthermore, improvement of the NYHA class was observed. Despite that, mean BNP levels remained unchanged (405.3 ± 133.9 vs. 596.5 ± 245.2 pg/mL, p = 0.191; after and before the procedure, respectively). In some patients with device located above the annulus level, an increase in BNP levels was observed.

Conclusions: BNP seems to be useless for the assessment of patients after PTMA. This may be related to mechanical stress on the annulus and atrial wall caused by the device itself.

Key words: BNP, percutaneous mitral annuloplasty, mitral regurgitation

INTRODUCTION

Functional mitral regurgitation (FMR), in contrast to rheumatic or degenerative MR, is primarily due to abnormalities of the ventricular muscle in the presence of normal mitral leaflets [1, 2]. There are many mechanisms that contribute to FMR, e.g. increased mitral tethering forces, reduction in closing forces, mechanical dyssynchrony, displacement of papillary muscles, and geometric changes in mitral annulus [3].

FMR is a common finding in heart failure (HF) patients that has important prognostic implications [3]. The severity of MR is an independent predictor of clinical outcome in this group of patients. Moreover, the available data suggests that even asymptomatic FMR has a negative impact on prognosis [4, 5].

Surgical valve repair is the standard method of treatment in patients with FMR. Unfortunately, cardiac surgery has a high procedural risk that limits its widespread application and results in low referral or high denial rates for mitral valve surgery [6]. Thus, percutaneous techniques for mitral valve repair are under development. One of the most advanced devices for percutaneous mitral annuloplasty (PTMA) is the Carillon™ device [7]. Results of available studies have revealed that per-
cutaneous mitral repair with the Carillon™ device is associated with improvements in quality of life, exercise tolerance, and selected echocardiographic parameters [8–10].

The B-type natriuretic peptide (BNP) assay has become one of the most important blood tests in cardiology that helps physicians diagnose HF, determine its severity, and estimate prognosis [11]. There is limited published data regarding the use of BNP assays in patients with MR as well as patients after restrictive mitral annuloplasty, and a lack of data regarding this issue in patients after PTMA [12–15].

We have previously reported that PTMA with the Carillon™ system improves echocardiographic parameters of FMR and results in a functional benefit to patients [9, 10]. However, it remains unclear which clinical parameter reflects the efficacy of the procedure and should be used to monitor its results.

The aim of this study was to assess the value of BNP assays in consecutive patients with FMR undergoing percutaneous mitral valve repair with the Carillon™ device and to evaluate if BNP levels correlate with functional improvements in this group of patients.

METHODS

Study population

Thirteen consecutive patients (eight males and five females, mean age 60.54 ± 1.95 years) with FMR who underwent successful implantation of the Carillon™ device were enrolled (baseline demographics are presented in Table 1). The inclusion criteria included FMR grade 2+ to 4+ due to dilated cardiomyopathy or ischaemic heart disease, type 1 regurgitation according to the Carpentier classification, New York Heart Association (NYHA) class II to IV, six-minute walk distance between 150 and 450 m, left ventricular ejection fraction (LVEF) < 40%, left ventricular end-diastolic diameter indexed for body surface area (LVEDD/BSA) > 3 cm/m², LVEDD > 55 mm and age > 18 years. All patients received standard-of-care HF drug therapy. The exclusion criteria included severe tricuspid regurgitation, organic mitral pathology, indications for surgical revascularisation, recent (< three months) hospitalisation due to myocardial infarction, coronary artery bypass graft surgery or unstable angina, percutaneous coronary intervention in the past 30 days, thrombus in the left atrial appendage, pacing lead in the coronary sinus, two anchors connected by a curved nitinol bridge [7] and after month after the implantation. All echocardiographic parameters 

<table>
<thead>
<tr>
<th>Device implantation, functional assessment and BNP assays</th>
</tr>
</thead>
</table>
| The anatomical relationship between the coronary venous system and the mitral annulus in most cases enables PTMA via the coronary sinus [16, 17]. The coronary sinus, great cardiac vein and the origin of the anterior interventricular vein surround the posterior mitral annulus. This prompted research into percutaneous approaches to mitral annuloplasty. The Carillon™ device is designed to be introduced into the coronary venous system and modify the shape of the mitral annulus. This catheter-based technique reduces valve leakage and thus decreases MR. The device is composed of two anchors connected by a curved nitinol bridge [7] and after being positioned in the coronary sinus and great cardiac vein, it exerts an external force on surrounding tissues, including the mitral annulus. The effect of the implanted system on the degree of MR is verified immediately after implantation by transthoracic echocardiography (TTE) performed in the catheterisation laboratory.

The six-minute walk test (6MWT), the Naughton treadmill exercise test, as well as plasma BNP levels were evaluated before the procedure and after one month. The venous blood samples were drawn from clinically stable patients and collected in EDTA containing tubes. Plasma BNP levels were measured using the AxSYM BNP assay (Abbott Laboratories, Abbott Park, IL, USA). Furthermore, TTE was performed one month after the implantation. All echocardiographic pa-
placement of the Carillon™ device above the mitral annulus level was observed in four patients in whom BNP levels rose after the procedure (mean 578 vs. 698 pg/mL).

**DISCUSSION**

The present study confirms our previous findings that the implantation of the Carillon™ device is associated with an improvement in functional and selected echocardiographic parameters [9, 10]. The current study included another cohort placement of the Carillon™ device above the mitral annulus level was observed in four patients in whom BNP levels rose after the procedure (mean 578 vs. 698 pg/mL).

**RESULTS**

PTMA with the Carillon™ device resulted in acute MR reduction. The TTE parameters of the MR significantly improved immediately after the procedure compared to the baseline, including vena contracta (0.35 ± 0.03 vs. 0.64 ± 0.03 cm, p < 0.05), effective regurgitant orifice area (EROA; 0.18 ± 0.02 vs. 0.32 ± 0.05 cm², p < 0.05), MR jet area/left atrial (LA) area (33.12 ± 2.06 vs. 47.06 ± 2.33%, p < 0.05) and right ventricle (RV) (23.98 ± 2.76 vs. 45.25 ± 7.47 mL, p < 0.05). Statistically significant improvement in echocardiographic parameters was maintained at one-month follow-up — vena contracta (0.31 ± 0.03 vs. 0.64 ± 0.03 cm, p < 0.05), EROA (0.2 ± 0.02 vs. 0.32 ± 0.05 cm², p < 0.05), MR jet area/LA area (32.33 ± 1.98 vs. 47.06 ± 2.33%, p < 0.05) and RV (27.84 ± 2.17 vs. 45.25 ± 7.47 mL, p < 0.05). Both the Naughton treadmill exercise test (3.12 ± 0.18 vs. 4.3 ± 0.45 min, p < 0.05), and the 6MWT (295.2 ± 13.4 vs. 320 ± 29.63 m, p < 0.05), improved after one month of follow-up. The NYHA functional classification was reduced from an average of 3.0 at baseline to 2.31 ± 0.17 at one month follow-up. While before the procedure all the patients were in NYHA class III, one month after the implantation 77% of patients reported an improvement of the above-mentioned functional parameter (Table 2). Despite improvement in functional capacity and echocardiographic indices, BNP levels remained unchanged (596.5 ± 245.2 vs. 405.3 ± 133.9 pg/mL, p = 0.191, for before and after the procedure, respectively) (Fig. 1). No correlations between changes in BNP levels and those in functional and echocardiographic parameters were found (one month follow-up vs. baseline) (Table 3). Furthermore, in some patients, despite functional and echocardiographic improvements, a marked increase in BNP levels was observed. In addition, a statistically non-significant trend toward higher improvement in functional and selected echocardiographic parameters [9, 10]. The current study included another cohort

<table>
<thead>
<tr>
<th>Variables</th>
<th>Correlation coefficient</th>
</tr>
</thead>
<tbody>
<tr>
<td>Δ BNP and Δ six-minute walk test</td>
<td>r = 0.29, p = 0.37</td>
</tr>
<tr>
<td>Δ BNP and Δ Naughton treadmill exercise test</td>
<td>r = 0.31, p = 0.33</td>
</tr>
<tr>
<td>Δ BNP and Δ effective regurgitant orifice area</td>
<td>r = 0.13, p = 0.68</td>
</tr>
<tr>
<td>Δ BNP and Δ right ventricle</td>
<td>r = 0.13, p = 0.66</td>
</tr>
<tr>
<td>Δ BNP and Δ vena contracta</td>
<td>r = 0.35, p = 0.24</td>
</tr>
<tr>
<td>Δ BNP and Δ MR jet area/LA area</td>
<td>r = 0.30, p = 0.31</td>
</tr>
</tbody>
</table>

Δ — difference between one-month follow-up and baseline; MR — mitral regurgitation; LA — left atrial
of patients, different from those previously reported [9, 10] and it is worth mentioning that both the echocardiographic and functional results of the procedure are similar to those previously reported.

It is unclear which clinical parameters do correlate with functional improvement of patients undergoing PTMA and may be used to evaluate the efficacy of the procedure. Our study demonstrates that BNP seems to be a useless biomarker for the assessment of patients after percutaneous mitral valvuloplasty with the Carillon™ device. To the best of our knowledge, this is the first study to address the association of BNP with echocardiographic and functional parameters in patients with FMR after percutaneous mitral valve repair.

BNP is known to be produced in human hearts [18–20]. The active hormone is cleaved from the precursor protein and then secreted into the bloodstream by cardiac ventricles in response to increased myocardial stretch [21, 22]. Many studies have revealed that BNP is a powerful prognostic marker in HF patients [23, 24].

Despite the number of publications documenting the prognostic value of BNP in patients with HF, there are few studies on its use in subjects with MR as well as those after restrictive mitral annuloplasty. Furthermore, there is no data regarding the use of BNP in patients undergoing PTMA. Sutton et al. [25] reported that BNP level increases with symptoms and severity of MR. The plasma levels of BNP rose with increasing LA dimensions, vena contracta width and regurgitant fraction. Thus, the researchers concluded that this may be an important marker in patients with this acquired valvular heart disease. In the study of Detaint et al. [14], elevated BNP was linked to a higher end-systolic volume index, irrespective of MR aetiology and symptoms. In another study, Paparella et al. [15] evaluated the potential benefit of restrictive annuloplasty with undersized mitral rings in patients with ischaemic MR. Six months after the operation, a significant reduction of BNP plasma levels was reported.

The results of the present study contrast with the above-mentioned findings. In our study, we found only a significant improvement in terms of echocardiographic (EROA, vena contracta, regurgitant volume and MR jet area/LA area) and functional (6MWTest, the Naughton treadmill exercise test and the NYHA classification) status, but without any significant reduction of BNP plasma values. Furthermore, despite echocardiographic and functional improvement, three patients showed increases in the BNP level. In those patients, the device was implanted within the great cardiac vein, which was placed above the mitral annulus level. There was also no correlation between changes in BNP levels and those in echocardiographic and functional parameters in the whole group studied.

There may be several explanations for these results. The Carillon™ device is implanted into the coronary venous system and applies tension to the mitral annulus in order to improve mitral leaflets’ coaptation [7]. The available data indicates that the course of the coronary sinus and the great cardiac vein is variable [17]. Usually, they travel along the posterior wall of the LA and superior to the mitral annulus, and it is rare for these vessels to travel exactly along the annulus in the atrioventricular groove. Hence, the implantation of the Carillon™ device affects not only the mitral annulus, but also the LA. We hypothesise that a lack of significant reduction in, or even an increase in, the BNP plasma level may be related to mechanical stress on the atrial wall. This is the more likely if we consider that in spite of the fact that BNP is thought to be specifically secreted from the ventricles, there have been reports suggesting that atria are also the source of BNP [26]. It has to be stressed that our observations suggest that in patients with Carillon™ device implanted into coronary veins located above the annulus level, the mean BNP levels tended to increase, although due to the small numbers in the study group the difference was statistically not significant. Another possible explanation is that PTMA with the Carillon™ device addresses only a few components of the complex pathophysiology of FMR. The latter includes not only geometric changes in the mitral annulus, but also increased mitral tethering forces, reduction in closing forces, mechanical dyssynchrony and displacement of papillary muscles [2, 3]. FMR is believed to be a consequence of left ventricle remodelling and annular dilation probably does not play a key role. It is also plausible that there might be a longer time lag between a successful procedure and the restoration of the ventricular function leading to a reduction in BNP levels.

**Limitations of the study**

Some of the limitations of our study need to be acknowledged. Because of the limited sample size, the interpretation of results should be cautious. A further limitation is that the study population was predominantly composed of patients with NYHA III class. In addition, longer observation is needed to confirm elevated BNP values, despite improvement in HF, as the dynamics of BNP changes may be slower.

**CONCLUSIONS**

BNP seems to be useless for the assessment of patients after PTMA. This may be related to mechanical stress on the annulus and atrial wall caused by the device itself.

**Acknowledgements**

This study was supported by Cardiac Dimensions Inc. (Kirkland, WA, USA).

**Conflict of interest**

TS was an investigator in clinical studies supported by Cardiac Dimensions Inc. (Kirkland, WA, USA).
References

Peptyd natriuretyczny typu B u pacjentów po przezskórnej annuloplastyce mitralnej z dostępu przez żyły serca

Tomasz Siminiak, Olga Jerzykowska, Michał Kuzemczak, Andrzej Szyszka, Piotr Kalmucki, Artur Baszko

Centrum Medyczne HCP, Uniwersytet Medyczny, Poznań

Streszczenie


Metody: Do badania włączono 13 kolejnych pacjentów po skutecznej PTMA z implantacją urządzenia Carillon™ do żył serca pod kontrolą echokardiografii. Przed zabiegiem, bezpośrednio po zabiegu i po miesiącu oceniano ponadto osoczowe stężenia BNP, wynik w 6-minutowym teście chodu (6MWT) oraz rezultat próby wysiłkowej.

Wyniki: U wszystkich pacjentów poddanych PTMA istotna poprawa w zakresie parametrów echokardiograficznych utrzymywała się również po miesiącu od zabiegu: talia fali zwrotnej (0,31 ± 0,03 vs. 0,64 ± 0,03 cm; p < 0,05), efektywna powierzchnia ujęcia fali zwrotnej (0,2 ± 0,02 vs. 0,32 ± 0,05 cm²; p < 0,05), pole powierzchni fali zwrotnej/pole powierzchni lewego przedsiomka (32,33 ± 1,98 vs. 47,06 ± 2,3%; p < 0,05) i objętość fali zwrotnej (27,84 ± 2,17 vs. 45,25 ± 7,47 ml; p < 0,05). Poprawie uległy także: czas trwania próby wysiłkowej (4,3 ± 0,45 vs. 3,12 ± 0,18 min; p < 0,05), 6MWT (320 ± 29,63 vs. 295,2 ± 13,4 m; p < 0,05) oraz wydolność krążenia wg skali NYHA. Mimo to średnie stężenia BNP się nie zmieniły (405,3 ± 133,9 vs. 596,5 ± 245,2 pg/ml; p = 0,191; odpowiednio po zabiegu i przed zabiegiem). U pacjentów, u których implantowane urządzenie znalazło się powyżej poziomu pierścienia mitralnego, stężenia BNP wzrosły.

Wnioski: Wartość BNP nie nadaje się do oceny pacjentów po PTMA, co może się wiązać z mechanicznym uciskiem urządzenia Carillon™ na ścianę przedsionka.

Słowa kluczowe: BNP, przeskórnna annuloplastyka mitralna, niedomykalność mitralna

Kardiol Pol 2014; 72, 5: 446–451

Adres do korespondencji:
prof. Tomasz Siminiak, Uniwersytet Medyczny im. Karola Marcinkowskiego, Pracownia Kardiologii Inwazyjnej, Centrum Medyczne HCP, ul. 28 Czerwca 1956 roku Nr 194, 61–485 Poznań, e-mail: tomasz.siminiak@usoms.poznan.pl

www.kardiologiapolska.pl