The significance of natriuretic peptide in treatment of pulmonary hypertension after mitral valve replacement

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Objectives: To compare the therapeutic efficacy of recombinant human brain natriuretic peptide and prostaglandin E1 in the treatment of pulmonary hypertension after mitral valve replacement.

Methods: Sixty patients with postoperative pulmonary hypertension were divided randomly into 3 groups that received saline, prostaglandin E1, and natriuretic peptide infusions for 12 hours each. The hemodynamics data were monitored consecutively, and the levels of thromboxane A2 and cyclic guanosine monophosphate were detected pretreatment, after treatment, and 1 week after surgery.

Results: The arterial pressure, pulmonary arterial pressure, and pulmonary capillary wedge pressure decreased 1 hour after prostaglandin E1 treatment and rebounded after treatment discontinuation. The pulmonary arterial pressure and pulmonary capillary wedge pressure in the natriuretic peptide group decreased 3 hours after treatment; pulmonary arterial pressure decreased less than that of the prostaglandin group, and there was no evidence of hemodynamic rebound after treatment discontinuation. The natriuretic peptide had no significant effects on arterial pressure. In both the prostaglandin and natriuretic peptide groups, cyclic guanosine monophosphate increased after the treatment, which was even higher in the latter group. Prostaglandin E1 could lead to the decrease of thromboxane A2, which was not seen in the natriuretic peptide group.

Conclusions: Both brain natriuretic peptide and prostaglandin E1 can effectively reduce pulmonary hypertension; however, natriuretic peptide has a slower and milder efficacy. The effects of these 2 drugs in reducing the pulmonary arterial pressure may be mediated through different pathways. (*J Thorac Cardiovasc Surg* 2014;147:1362-7)

Most patients who have mitral valve disease combined with pulmonary hypertension suffer persistent pulmonary hypertension after their valve replacement¹ because of their previous pulmonary arteriole fibrosis and the release of inflammatory factors caused by surgical trauma and cardiopulmonary bypass.^{2,3} Pulmonary hypertension can increase afterload of the right heart chamber, causing cardiac events and affecting survival after surgery^{4,5}; thus correct selection of effective drugs to reduce pulmonary arterial pressure (PAP) has important clinical significance. Brain natriuretic peptide (BNP) is a polypeptide secreted by the ventricles that can resist cardiac volume and pressure load and regulate vascular tone. In recent years, recombinant human BNP (rhBNP) has been used in clinical practice, but its PAP-lowering effect after cardiac surgery has no exact statistical data. Considering that its action time and metabolic time are similar to prostaglandin E1

(PGE1), which is used commonly in clinical practice at present,^{6,7} we compared the pharmacodynamics of the 2 drugs in the short term after surgery. A number of studies have shown that thromboxane A2 (TXA2) and cyclic guanosine monophosphate (cGMP) play important roles in the regulation of pulmonary vasoconstriction.^{8,9} In this study, the mechanisms of the 2 drugs in lowering PAP were compared further by detecting the concentration changes in TXA2 and cGMP before and after treatment.

METHODS

Study Design and Patient Selection

Patients who received mitral valve replacement (MVR) during cardiopulmonary bypass in the Cardiac Center of Tianjin Chest Hospital from March 2011 to May 2012 were included in this study. After surgery, a total of 60 patients with a mean PAP (MPAP) of 25 mm Hg or higher (measured by using the CCombo Swan-Ganz catheter; Edwards LifeSciences, Irvine, Calif) were enrolled randomly in this study. In particular, patients with unstable hemodynamics (systolic arterial pressure < 60 mm Hg, pulmonary artery systolic pressure > 70 mm Hg, or low cardiac output syndrome) who needed multiple drugs for treatment were ruled out.

After the surgery, the patients were transferred to the intensive care unit (ICU), assisted by ventilators, and received dopamine and other vasoactive drugs to maintain their basic vital signs in a stable state. All the enrolled patients were divided randomly into 3 groups: the control group, in which patients received a continuous infusion of saline at 5 mL/h for 12 hours; the rhBNP group, in which patients first received an intravenous injection of rhBNP at 2 µg/kg, and then received a continuous infusion at 0.01 µg/kg/min for 12 hours; and the PGE1 group, in which patients received a continuous infusion of PGE1 at 30 ng/kg/min for 12 hours.

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Abbreviations and Acronyms

BNP	= brain natriuretic peptide
cGMP	= cyclic guanosine monophosphate
ELISA	= enzyme-linked immunosorbent assay
ICU	= intensive care unit
MAP	= mean radial arterial pressure
MPAP	= mean pulmonary arterial pressure
MVR	= mitral valve replacement
PAP	= pulmonary arterial pressure
PCWP	= pulmonary capillary wedge pressure
PGE1	= prostaglandin E1
PVRI	= pulmonary vascular resistance index
rhBNP	= recombinant human brain natriuretic peptide
TXA2	= thromboxane A2

The mean radial arterial pressure (MAP), MPAP, pulmonary capillary wedge pressure (PCWP), cardiac output index, and pulmonary vascular resistance index (PVRI) data were measured with a Philips IntelliVue mp40 monitor (Philips Medical Systems, Irvine, Calif) at the following time points: before treatment, at 1, 3, 6, and 12 hours after treatment, and 2 hours after treatment discontinuation. Whole blood samples were collected from the peripheral venous blood of the patients before treatment, 2 hours after discontinuation of the drugs, as well as 1 week after surgery (Figure 1). The enzyme-linked immunosorbent assay (ELISA) method was used to detect the cGMP and TXA2 concentrations. The Human cGMP ELISA and Human TXA2 ELISA kits were manufactured by Shanghai Blue-Gene Biotech Co, Ltd (Shanghai, China).

All the groups were double-blinded, and no nitric oxide, PDE inhibitors, or similar drugs were given to patients in the study. The study was terminated in case of any severe hypotension, severe pulmonary hypertension, heart failure, and so forth, and other drugs should be used to treat these conditions accordingly. The Medical Ethics Committee of Tianjin and the Institutional Review Board of Tianjin Medical University approved the study, and all patients signed written informed consent before study initiation.

Statistical Analysis

All data were tested via a one-sample Kolmogorov-Smirnov test for normality. If the P value was greater than .10 the data were considered to be normal distributions, which were expressed as the mean $\pm$ standard deviation, whereas non-normal distributions were expressed as the median $\pm$ quartile.

For normal distributions, the metrologic data within the same group at different time points were analyzed via one-way analysis of variance followed by the Student–Newman–Keuls test to compare the means of independent groups. Non-normally distributed data were analyzed via the rank-sum test.

The Pearson correlation was used to examine the extent of the correlations between related parameters. A P value of less than .05 was considered statistically different.

RESULTS

Patient Characteristics

There were no significant differences among the 3 groups in the preoperative demographics and intraoperative

FIGURE 1. Design of the study. TXA2, Thromboxane A2; cGMP, cyclic guanosine monophosphate; PGE1, prostaglandin E1; MVR, mitral valve replacement; PH, pulmonary hypertension; rhBNP, recombinant human brain natriuretic peptide.

variables including cardiopulmonary bypass time, cross-clamping time, mitral valve gradient after replacement, and so forth ($P > .05$). No significant differences were observed in the inotrope score (dopamine dose [$\mu\text{g/kg/min}$] + dobutamine dose [$\mu\text{g/kg/min}$] + $100 \times$ epinephrine dose [$\mu\text{g/kg/min}$] + $100 \times$ norepinephrine dose [$\mu\text{g/kg/min}$]) in the ICU ($P > .05$), whereas the postoperative ventilator-assisted duration in the PGE1 group was shorter than in the control groups ($P < .05$) (Table 1).

All the nurses and doctors followed the procedures strictly and obtained the hemodynamic and laboratory data punctually. One patient in the control group had an MPAP greater than 70 mm Hg and signs of right heart

FIGURE 2. A, $P < .05$ compared with the T1 group. B, $P < .05$ compared with the T2 group. C, $P < .05$ compared with the T3 group. D, $P < .05$ compared with the T4 group. E, $P < .05$ compared with the T5 group. * $P < .05$ compared with the control group. # $P < .05$ compared with the PGE1 group. T1, After surgery and pretreatment; T2, 1 hour after treatment; T3, 3 hours after treatment; T4, 6 hours after treatment; T5, 12 hours after treatment; T6, 2 hours after treatment discontinuation; PGE1, prostaglandin E1; rhBNP, recombinant human brain natriuretic peptide; MAP, mean radial arterial pressure.

FIGURE 3. A, $P < .05$ compared with the T1 group. B, $P < .05$ compared with the T2 group. C, $P < .05$ compared with the T3 group. D, $P < .05$ compared with the T4 group. E, $P < .05$ compared with the T5 group. * $P < .05$ compared with the control group. # $P < .05$ compared with the PGE1 group. T1, After surgery and pretreatment; T2, 1 hour after treatment; T3, 3 hours after treatment; T4, 6 hours after treatment; T5, 12 hours after treatment; T6, 2 hours after treatment discontinuation; PGE1, prostaglandin E1; rhBNP, recombinant human brain natriuretic peptide; MPAP, mean pulmonary arterial pressure.

failure 3 hours after the surgery. The patient was treated with nitric oxide inhalation, milrinone, and PGE1 infusion. The laboratory data from this patient were excluded. The other 59 patients finished the study and there were no missing data points.

Homodynamic Data

MAP data. Intragroup comparison. The MAP of the PGE1 group had decreased since 1 hour after treatment (79.3 ± 11.4 to 71.2 ± 12.5 mm Hg) ($P < .05$), and recovered to the initial level at 6 hours after treatment (76.8 ± 11.3 mm Hg) ($P > .05$). However, it tended to rebound after treatment discontinuation (78.2 ± 9.6 to 84.3 ± 13.4 mm Hg) ($P < .05$). No similar variations in the MAP were observed in the control group and the rhBNP group.

Intergroup comparison. During 1 to 3 hours after treatment, the level of MAP in the PGE1 group was lower than in the control group and the rhBNP group (1 hour: 71.2 ± 12.5 vs 78.8 ± 9.8 , 81.3 ± 8.1 mm Hg; 3 hours: 73.8 ± 10.6 vs 82.0 ± 8.9 , 79.1 ± 9.3 mm Hg, respectively) ($P < .05$). During 6 to 12 hours after treatment, there were no significant differences among the 3 groups in MAP

($P > .05$). The level of MAP in the PGE1 group was higher than those in the other 2 groups at 2 hours after treatment discontinuation (84.3 ± 13.4 vs 80.4 ± 10.3 , 78.0 ± 12.2 mm Hg, respectively) ($P < .05$) (Figure 2).

MPAP data. Intragroup comparison. The MPAP of the PGE1 group decreased drastically at 1 hour after treatment (32.7 ± 7.6 to 21.9 ± 11.4 mm Hg) ($P < .05$), and increased slightly at 3 hours after treatment (3 hours: 23.8 ± 10.1 mm Hg) ($P < .05$), however, it was still lower than the MPAP level at pretreatment ($P < .05$). It tended to rebound at 2 hours after treatment discontinuation (27.9 ± 8.0 mm Hg) ($P < .05$). The MPAP of the rhBNP group decreased at 3 hours after treatment (33.1 ± 6.1 to 27.6 ± 6.4 mm Hg) ($P < .05$), and stayed stable until 2 hours after treatment discontinuation ($P > .05$). There was no significant change during the trial in the control group ($P > .05$).

Intergroup comparison. The level of MPAP in the PGE1 group was lower than that in the rhBNP group at 1, 3, and 6 hours after treatment (1 hour: 21.9 ± 11.4 vs 30.8 ± 8.9 mm Hg; 3 hours: 23.8 ± 10.1 vs 27.6 ± 6.4 mm Hg; 6 hours: 24.8 ± 9.7 vs 26.9 ± 8.5 mm Hg, respectively) ($P < .05$). There were no significant differences between the PGE1 group and the rhBNP group at 12 hours after treatment (25.5 ± 8.8 vs 25.4 ± 9.2 mm Hg, respectively) ($P > .05$) (Figure 3).

PCWP data. Intragroup comparison. The PCWP of the PGE1 group decreased 1 hour after treatment (21.6 ± 8.7 to 13.5 ± 5.6 mm Hg) ($P < .05$), and increased slightly 3 hours after treatment (16.3 ± 6.1) ($P < .05$), then stayed stable at this level. It returned to the pretreatment level 2 hours after treatment discontinuation ($P > .05$). The PCWP of the rhBNP group had decreased since 3 hours after treatment (20.7 ± 5.8 to 17.7 ± 4.2 mm Hg) ($P < .05$), without significant fluctuation until the end of the trial ($P > .05$). There was no significant change during the trial in the control group ($P > .05$).

Intergroup comparison. After the onset of the 2 drugs, the level of PCWP in the PGE1 group was similar to the rhBNP group (3 hours: 16.3 ± 6.1 vs 17.7 ± 4.2 mm Hg; 6 hours: 16.2 ± 6.9 vs 17.0 ± 4.1 mm Hg; 12 hours: 17.0 ± 7.0 vs 16.6 ± 6.5 mm Hg, respectively) ($P > .05$) (Figure 4).

Cardiac output index data. Intragroup comparison. No significant fluctuations were observed during the trial in all 3 groups ($P > .05$).

TABLE 1. Patient characteristics

Groups	Sex, M/F	Age, y	Hypertension, Y/N	Diabetes, Y/N	Smoking, Y/N	Atrial fibrillation, Y/N	Stenosis/regurgitation/ combination
Control group	11/9	56 ± 7	3/17	1/19	11/9	13/7	4/5/11
PGE1 group	9/11	56 ± 9	2/18	0/20	10/10	14/6	5/5/10
rhBNP group	13/7	57 ± 7	3/17	0/20	11/9	15/5	7/2/11

M, Male; F, female; Y, yes; N, no; CPB, cardiopulmonary bypass; MV, mitral valve; ICU, intensive care unit; PGE1, prostaglandin E1; rhBNP, recombinant human brain natriuretic peptide. * $P < .05$ compared with the control group.

FIGURE 4. A, $P < .05$ compared with the T1 group. B, $P < .05$ compared with the T2 group. C, $P < .05$ compared with the T3 group. D, $P < .05$ compared with the T4 group. E, $P < .05$ compared with the T5 group. * $P < .05$ compared with the control group. # $P < .05$ compared with the PGE1 group. T1, After surgery and pretreatment; T2, 1 hour after treatment; T3, 3 hours after treatment; T4, 6 hours after treatment; T5, 12 hours after treatment; T6, 2 hours after treatment discontinuation; PGE1, prostaglandin E1; rhBNP, recombinant human brain natriuretic peptide; PCWP, pulmonary capillary wedge pressure.

Intergroup comparison. No significant differences were observed at each time point among the 3 groups ($P > .05$) (Figure 5).

PVRI data. Intragroup comparison. The PVRI of the PGE1 group decreased drastically 1 hour after treatment (231.7 ± 114.2 to 163.9 ± 120.6 dynes/s/cm⁵/m²) ($P < .05$), then stayed stable at this level. It tended to rebound 2 hours after treatment discontinuation (219.5 ± 47.8 dynes/s/cm⁵/m²) ($P < .05$). The PVRI of the rhBNP group decreased 1 hour after treatment (245.3 ± 40.7 to 210.7 ± 51.0 dynes/s/cm⁵/m²) ($P < .05$), and decreased further 3 hours after treatment (186.5 ± 55.5 dynes/s/cm⁵/m²) ($P < .05$), then stayed stable until the end of the trial ($P > .05$). There was no significant change during the trial in the control group ($P > .05$).

Intergroup comparison. The level of PVRI in the rhBNP group was lower than the control group but higher than the PGE1 group at 1 and 3 hours after treatment ($P < .05$). There were no significant differences between the PGE1 group and the rhBNP group at 6 and 12 hours after treatment ($P > .05$), and both groups were higher than the control group during this time ($P < .05$). The level of the rhBNP group was lower than that of the PGE1 group and the control group at 2 hours after treatment discontinuation ($P < .05$) (Figure 6).

FIGURE 5. T1, After surgery and pretreatment; T2, 1 hour after treatment; T3, 3 hours after treatment; T4, 6 hours after treatment; T5, 12 hours after treatment; T6, 2 hours after treatment discontinuation; PGE1, prostaglandin E1; rhBNP, recombinant human brain natriuretic peptide; CI, cardiac output index.

TXA2 and cGMP Levels

TXA2 data. Intragroup comparison. In the control group, the TXA2 level decreased 1 week after surgery ($P < .05$), whereas there were no significant changes in the perioperative period ($P > .05$). In the PGE1 group the TXA2 level after treatment was lower than that of pretreatment ($P < .05$), and it decreased further 1 week after surgery ($P < .05$). In the rhBNP group no significant change was observed before and after treatment ($P > .05$), however, the TXA2 level decreased at 1 week after surgery ($P < .05$).

Intergroup comparison. There were no significant differences among the 3 groups in the TXA2 level at pretreatment and 1 week after surgery ($P > .05$). The level of the PGE1 group was lower than those of the control group and the rhBNP group after treatment ($P < .05$) (Table 2).

cGMP data. Intragroup comparison. In the control group the cGMP level increased 1 week after surgery ($P < .05$), whereas there were no significant changes in the perioperative period ($P > .05$). In the PGE1 group the cGMP level increased after treatment ($P < .05$), and it increased further 1 week after surgery ($P < .05$). In the rhBNP group the cGMP level increased drastically after treatment ($P < .05$). At 1 week after surgery it decreased, but was still higher compared with pretreatment levels ($P < .05$) (Table 3).

Intergroup comparison. There were no significant differences among the 3 groups in the cGMP level at pretreatment and 1 week after surgery ($P > .05$). The level of

TABLE 1. Continued

Cholesterol level, mmol/L	CPB time, min	Cross-clamping time, min	Intraoperative blood loss	Postoperative mean MV gradient, mm Hg	Postoperative ventilator-assisted time, h	Inotrope score in the ICU
4.78 ± 1.42	112 ± 33	58 ± 13	278 ± 57	6.7 ± 3.4	46 ± 25	6.4 ± 2.1
4.46 ± 1.22	121 ± 54	62 ± 19	293 ± 70	7.2 ± 3.1	37 ± 29*	6.9 ± 2.7
4.57 ± 1.77	117 ± 37	56 ± 16	288 ± 64	6.9 ± 3.6	42 ± 30	6.1 ± 2.5

FIGURE 6. A, $P < .05$ compared with the T1 group. B, $P < .05$ compared with the T2 group. C, $P < .05$ compared with the T3 group. D, $P < .05$ compared with the T4 group. E, $P < .05$ compared with the T5 group. * $P < .05$ compared with the control group. # $P < .05$ compared with the PGE1 group. T1, After surgery and pretreatment; T2, 1 hour after treatment; T3, 3 hours after treatment; T4, 6 hours after treatment; T5, 12 hours after treatment; T6, 2 hours after treatment discontinuation; PGE1, prostaglandin E1; rhBNP, recombinant human brain natriuretic peptide; PVRI, pulmonary vascular resistance index.

the PGE1 group was higher than that of the control group, but lower than that of the rhBNP group after treatment ($P < .05$).

The cGMP concentration was correlated negatively with MPAP after treatment ($r = -0.63$, $P < .05$). However, no significant correlation was observed between the cGMP concentration and MPAP at pretreatment. The TXA2 concentration had no significant correlation with MPAP either.

DISCUSSION

Pulmonary hypertension caused by mitral stenosis or mitral incompetence belongs to type 2 pulmonary hypertension (left heart system disease-induced pulmonary hypertension). According to the European Society of Cardiology/European Respiratory Society guidelines¹⁰ published in 2009, in the short-term therapy of postoperative pulmonary hypertension, prostaglandin was listed as a grade I-A drug to treat the nonvasoreactive pulmonary hypertension in stages III and IV patients (World Health Organization-functional class); the PAP-lowering effect of rhBNP, however, was not mentioned. Our study indicated that the PAP-lowering action of rhBNP was slower and milder compared with PGE1. Moreover, we found that PGE1 reduced the PAP and simultaneously caused

TABLE 3. cGMP data (pg/mL)

Groups	T1	T2	T3
Control group	10.7 ± 7.6	11.1 ± 8.4	21.1 ± 15.2*,†
PGE1 group	11.3 ± 8.3	18.5 ± 13.3*,‡	22.5 ± 18.4*,†
rhBNP group	9.9 ± 8.7	33.8 ± 20.1*,†,§	23.6 ± 19.9*,†

T1, Pretreatment after surgery; T2, 2 hours after discontinuation of the drugs; T3, 1 week after surgery; PGE1, prostaglandin E1; rhBNP, recombinant human brain natriuretic peptide. * $P < .05$ compared with the T1 group. † $P < .05$ compared with the T2 group. ‡ $P < .05$ compared with the control group. § $P < .05$ compared with the PGE1 group.

the decrease in systemic vascular resistance, however, the PAP tended to rebound after the treatment discontinuation. This behavior was not observed in the rhBNP group. Thus, the result suggested that rhBNP is suitable to treat patients with hemodynamic instability, especially low blood pressure, and PGE-1 has obvious effects in controlling the acute pulmonary hypertension crisis. At present, no similar studies have been conducted in which continuous hemodynamic monitoring is performed during rhBNP treatment. The results from the current study may provide a reference for further studies about the rhBNP action time. In terms of the effects on decreasing PAP, Michaels et al¹¹ proposed that the infusion of rhBNP for 30 minutes could reduce the MPAP by 29% and PVRI by 35% for patients with postcapillary pulmonary hypertension (MPAP ≥ 25 mm Hg; PCWP > 15 mm Hg) at a rest stage. In the current study, most of the patients also had postcapillary pulmonary hypertension, but the efficacy was lower than the data reported by Michaels et al.¹¹ The discrepancy may be related to the pulmonary vascular ischemia-reperfusion injury after the cardiopulmonary bypass surgery, leading to a decrease of the reactivity.² Although PGE1 and rhBNP could decrease PAP and PVRI, the drugs had no significant effect on cardiac output index. It might be owing to multiple factors such as blood volume, heart rhythm, and so forth.

The decreased TXA2 and increased cGMP concentrations after the application of PGE1 suggest that the vasodilating effects may be mediated through different pathways. Reports about the effects of PGE1 on reducing the TXA2 level are available.⁸ Fortier et al¹² also proposed that prostacyclin could increase cyclic adenosine monophosphate levels in Landrace swine. Therefore, studies with a large scale of cases in human beings are required to confirm the direct effect of PGE1 on the cGMP pathway. The present study results indicated that rhBNP only affects the guanosine triphosphate-cGMP pathway, but the increase of cGMP was higher than that of PGE1, suggesting that the guanylate cyclase receptors are more sensitive to BNP compared with PGE1 (the guanylate cyclase can catalyze guanosine triphosphate to convert guanosine triphosphate into cGMP). Compared with the study performed by Khush et al,¹³ the decrease

TABLE 2. TXA2 data (pg/mL)

Groups	T1	T2	T3
Control group	442 ± 265	418 ± 295	280 ± 104*,†
PGE1 group	455 ± 220	309 ± 199*,‡	268 ± 114*,†
rhBNP group	424 ± 269	402 ± 281§	288 ± 166*,†

T1, Pretreatment after surgery; T2, 2 hours after discontinuation of the drugs; T3, 1 week after surgery; PGE1, prostaglandin E1; rhBNP, recombinant human brain natriuretic peptide. * $P < .05$ compared with the T1 group. † $P < .05$ compared with the T2 group. ‡ $P < .05$ compared with the control group. § $P < .05$ compared with the PGE1 group.

of MPAP is smaller with the application of rhBNP, whereas the increase of cGMP is similar (in the study results obtained by Khush et al,¹³ patients with postcapillary pulmonary hypertension at a resting state received continuous infusion of rhBNP for 30 minutes and their MPAP decreased by 29 mm Hg $\pm$ 11 mm Hg, whereas the cGMP in the peripheral blood increased by 341%). Therefore, pulmonary vascular injury after cardiopulmonary bypass can reduce the activity of the lower-level pathways of cGMP. However, it has a weak effect on the synthesis of cGMP after receiving BNP stimulation.

As a result, the concentrations of cGMP and TXA2 in the PGE1 and rhBNP groups had no significant differences compared with the control group 1 week after treatment, which indicated that although the short-term application of PGE1 and rhBNP after surgery can reduce the PAP and shorten the postoperative ventilator-assisted duration, the continuous PAP control with a long-term oral medication is still necessary if patients continue to have serious postoperative pulmonary hypertension.

Limitations

To review, almost all the patients in this study received different doses of dopamine or diuretics in the ICU, which inevitably affected the hemodynamics and caused bias in data collection. Because of the small sample size, the effect of rhBNP on pulmonary hypertension was not shown accurately in this study, which probably can be clarified further with a larger sample size.

CONCLUSIONS

RhBNP effectively can reduce the PAP after an MVR surgery. However, it works slower and more mildly compared with PGE1 for different mechanisms. Both rhBNP and PGE1 have no long-term effects owing to their short

metabolic duration. The long-term PAP-lowering application is still required for MVR patients after discharge.

References

1. Winterhalter M, Antoniou T, Loukanov T. Management of adult patients with perioperative pulmonary hypertension: technical aspects and therapeutic options. *Cardiology*. 2010;116:3-9.
2. Shann KG, Likosky DS, Murkin JM, Baker RA, Baribeau YR, DeFoe GR, et al. An evidence-based review of the practice of cardiopulmonary bypass in adults: a focus on neurologic injury, glycemic control, hemodilution, and the inflammatory response. *J Thorac Cardiovasc Surg*. 2006;132:283-90.
3. Prondzinsky R, Knüpfer A, Loppnow H, Redling F, Lehmann DW, Stabenow I, et al. Surgical trauma affects the proinflammatory status after cardiac surgery to a higher degree than cardiopulmonary bypass. *J Thorac Cardiovasc Surg*. 2005;129:760-6.
4. Kainuma S, Taniguchi K, Toda K, Funatsu T, Kondoh H, Nishino M, et al. Pulmonary hypertension predicts adverse cardiac events after restrictive mitral annuloplasty for severe functional mitral regurgitation. *J Thorac Cardiovasc Surg*. 2011;142:783-92.
5. Ghoreishi M, Evans CF, DeFilippi CR, Hobbs G, Young CA, Griffith BP, et al. Pulmonary hypertension adversely affects short- and long-term survival after mitral valve operation for mitral regurgitation: implications for timing of surgery. *J Thorac Cardiovasc Surg*. 2011;142:1439-52.
6. Gupta V, Rawat A, Ahsan F. Feasibility study of aerosolized prostaglandin E1 microspheres as a noninvasive therapy for pulmonary arterial hypertension. *J Pharm Sci*. 2010;99:1774-89.
7. Kimura K, Yamaguchi Y, Horii M, Kawata H, Yamamoto H, Uemura S, et al. ANP is cleared much faster than BNP in patients with congestive heart failure. *Eur J Clin Pharmacol*. 2007;63:699-702.
8. Hanazaki K, Kuroda T, Kajikawa S, Amano J. Prostaglandin E1 reduces thromboxane A2 in hepatic ischemia-reperfusion. *Hepatogastroenterology*. 2000;47:807-11.
9. Fei XW, Pan CJ, He YL, Fang YJ, Zhuang JL, Mei YA. Brain natriuretic peptide modulates the delayed rectifier outward K(+) current and promotes the proliferation of mouse Schwann cells. *J Cell Physiol*. 2011;226:440-9.
10. ESC, ERS, ISHLT, Gal N, Hoeper MM, Humbert M, et al. Guidelines for the diagnosis and treatment of pulmonary hypertension. *Eur Respir J*. 2009;34:1219-63.
11. Michaels AD, Chatterjee K, De Marco T. Effects of intravenous nesiritide on pulmonary vascular hemodynamics in pulmonary hypertension. *J Card Fail*. 2005;11:425-31.
12. Fortier S, DeMaria RG, Lamarche Y, Malo O, Denault A, Desjardins F, et al. Inhaled prostacyclin reduces cardiopulmonary bypass-induced pulmonary endothelial dysfunction via increased cyclic adenosine monophosphate levels. *J Thorac Cardiovasc Surg*. 2004;128:109-16.
13. Khush KK, De Marco T, Vakharia KT, Harmon C, Fineman JR, Chatterjee K, et al. Nesiritide acutely increases pulmonary and systemic levels of nitric oxide in patients with pulmonary hypertension. *J Card Fail*. 2006;12:507-13.