Comparative hemodynamic effects of vasopressin and norepinephrine after milrinone-induced hypotension in off-pump coronary artery bypass surgical patients

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Abstract

Objective: Phosphodiesterase inhibitor is essential to the pharmacologic management of decompensated heart failure because it increases contractility and decreases afterload of right ventricle. It also improves hemodynamics and increases blood flow of the grafted internal mammary arteries and middle cerebral arteries during coronary artery bypass surgery. However, it induces vasodilation and necessitates the use of vasoconstrictors, such as norepinephrine. We hypothesized that vasopressin could recover hypotension induced by milrinone with less effect on pulmonary vascular resistance (PVR) compared to norepinephrine.

Methods: Fifty patients, undergoing coronary artery bypass graft (CABG) surgery, were assigned randomly in a double-blind manner to receive either vasopressin or norepinephrine. After baseline hemodynamic measurements, a loading dose of milrinone 50 μg/kg was infused slowly for 20 min followed by continuous infusion of 0.5 μg/(kg min). Immediately after the loading dose of milrinone, hemodynamic variables were measured, and vasopressin (VP group) or norepinephrine (NE groups) was infused. After being titrated until the mean arterial pressure was increased by 20%, hemodynamic variables were measured again.

Results: Milrinone infusion reduced both systemic vascular resistance (SVR, 1218 ± 299 dyne s/cm² vs 838 ± 209 dyne s/cm², 1345 ± 299 dyne s/cm² vs 1011 ± 195 dyne s/cm²) and PVR (95 ± 34 dyne s/cm² vs 72 ± 30 dyne s/cm², 119 ± 85 dyne s/cm² vs 87 ± 33 dyne s/cm²) in the VP and NE groups, respectively. Vasopressin and norepinephrine infusion increased both SVR (838 ± 209 dyne s/cm² vs 1100 ± 244 dyne s/cm², 1011 ± 195 dyne s/cm² vs 1446 ± 681 dyne s/cm², respectively) and PVR (72 ± 30 dyne s/cm² vs 84 ± 18 dyne s/cm², 87 ± 33 dyne s/cm² vs 139 ± 97 dyne s/cm², respectively). The PRV/SVR ratio was decreased after vasopressin infusion (0.10 ± 0.03 vs 0.08 ± 0.03), while no changes were found after norepinephrine infusion (0.09 ± 0.02 vs 0.09 ± 0.02). Conclusions: In the patients undergoing CABG surgery, both norepinephrine and low dose vasopressin were effective in restoring milrinone-induced decrease of SVR. However, only low-dose vasopressin decreased the PVR/SVR ratio that was increased by milrinone. Considering the importance of maintaining systemic perfusion pressure as well as reducing right heart afterload, milrinone—vasopressin may provide better hemodynamics than milrinone—norepinephrine during the management of right heart failure.

Keywords: Milrinone; Norepinephrine; Off-pump coronary artery bypass surgery; Vasopressin

1. Introduction

Milrinone, a type III phosphodiesterase inhibitor, functions as an inotropic agent and a vasodilator. It may increase the contractility and decrease the afterload of right ventricle and therefore has often been used for the management of right heart failure. However, milrinone frequently causes excessive systemic vasodilation [1,2], and maintaining the systemic pressure is as important as reducing the right ventricular afterload in the management of right heart failure [3,4]. Thus, milrinone therapy often requires vasoconstrictors to prevent unwanted arterial hypotension. Although catecholamine vasopressors have been frequently used to treat milrinone-induced hypotension, they do not have selectivity on systemic vessels and may increase pulmonary vascular resistance (PVR) and right ventricular afterload.

Vasopressin has been reported to be effective in restoring the arterial pressure of milrinone-induced hypotension [5], postcardiotomy hypotension [6], and vasodilating septic shock [7]. By contrast, low-dose vasopressin has little effect...
on the patients with normal cardiovascular function [8]. It has different mechanisms of action compared to catecholamine vasopressors. Studies have shown that vasopressin decreases pulmonary artery pressure (PAP) both in normal and hypoxic conditions [9,10]. However, these findings were demonstrated only in animals or in vitro models.

We hypothesized that low-dose vasopressin could selectively recover the decreased systemic vascular resistance (SVR) caused by milrinone with a reduced effect on PVR in contrast to norepinephrine. In this double-blind study, we compared the changes of PVR, SVR and PVR/SVR ratio after administration of vasopressin or norepinephrine during milrinone-induced hypotension in patients undergoing coronary artery bypass graft (CABG) surgery.

2. Methods

After approval by the Institutional Review Board and having obtained informed consent, 52 unpremedicated patients scheduled for elective CABG were included in this prospective study. Patients with a left ventricular ejection fraction less than 35%, preoperative or intraoperative use of vasoactive drugs, more than mild mitral regurgitation, mean pulmonary artery pressure (MPAP) >25 mmHg on the preoperative echocardiography or cardiac catheterization and unstable angina were excluded.

Before surgery, patients were allocated into two groups by random drawing of a sealed envelope [vasopressin (VP), norepinephrine (NE)]. Vasopressin and norepinephrine infusions were prepared by another researcher not involved in the patient care. The allocation of patients to group vasopressin or norepinephrine was blinded to the surgeon and attending anesthesiologist. Anesthesia and surgery were conducted by the same anesthesiologist and surgeon in all cases.

In the operating room, patients received routine monitoring consisting of a five-lead electrocardiography with ST-segment analysis, radial arterial pressure, pulse oximetry, capnography, nasopharyngeal temperature, and urine output. Anesthesia was induced with midazolam (0.1 mg/kg), etomidate (0.15 mg/kg), sufentanyl (3 μg/kg), and vecuronium (1–1.5 mg/kg). Anesthesia was maintained until the end of operation with continuous infusions of midazolam (0.05 mg/(kg h)), sufentanyl (2.5 μg/(kg h)), and vecuronium (0.1 mg/(kg h)). A pulmonary artery catheter (Swan–Ganz CCOmbo CCO/SvO2, Edwards Lifesciences, PR, USA) was inserted through right internal jugular vein. Then, a transesophageal echocardiography probe was placed into the esophagus.

Before starting the study, additional fluid was infused to maintain more than 10 mmHg of pulmonary capillary wedge pressure (PCWP) when it dropped below 10 mmHg. The mechanical ventilator was set to maintain 40 mmHg of PaCO2 using arterial blood gas analysis. Temperature was measured continuously with a pulmonary artery catheter and was corrected above 36 °C by warm fluid administration.

When hemodynamic parameters were stabilized during the preparation of graft vessels, baseline hemodynamic variables were measured and a loading dose of milrinone 50 μg/kg was infused slowly for 20 min followed by continuous infusion of 0.5 μg/(kg min). Just after the loading dose of milrinone, hemodynamic variables were measured, and the continuous infusion of vasopressin or norepinephrine was started. The concentrations of vasopressin (0.171 unit/ml) and norepinephrine (0.286 μg/ml) were chosen so that the starting infusion volume was 7 ml/h. This corresponded to vasopressin 0.02 units/min and norepinephrine 2 μg/min. The maximum infusion rate allowed in this study was 56 ml/h, which corresponded to vasopressin 0.16 units/min and norepinephrine 16 μg/min. During the study, the drugs were titrated (infusion increased by 7 ml/h every 5–10 min) to maintain about 20% increase of mean arterial pressure (MAP) by an independent anesthesiologist blinded to the type of drug. The following hemodynamic variables were measured again at least 40 min after the start of vasopressin or norepinephrine infusion: heart rate (HR), MAP, central venous pressure (CVP), MPAP, cardiac output (CO), PCWP, SVR, PVR, and PVR/SVR. The CO was measured using thermodilution method.

Data are expressed as means ± SD or median (range). Demographic data were analyzed using the unpaired t-test. Comparison of several means following treatment was performed using repeated-measures analysis of variance and paired t-test with Bonferroni correction. The changes of hemodynamic variables between the two groups were compared using the unpaired t-test with Bonferroni correction. A P-value <.05 was considered significant. All analyses were conducted with SPSS version 11.0.

3. Results

Two out of the 52 patients had severe hypotension during milrinone loading. The attending anesthesiologist stopped the study and these patients were excluded from the data analysis. Demographic data are given in Table 1. There were no significant differences between the two groups. The median infusion rates of vasopressin and norepinephrine were 0.06 units/min (25th percentile, 0.04 units/min; 75th percentile, 0.09 units/min) and 7.5 μg/min (25th percentile, 5.2 μg/min; 75th percentile, 12.4 μg/min), respectively.

Milrinone infusion increased CO while it decreased MAP, SVR, and PVR. SVR was reduced from 1218 ± 185 dyne s/cm5 to 1011 ± 195 dyne s/cm5 (P < 0.0001), and from 1345 ± 299 dyne s/cm5 to 1011 ± 195 dyne s/cm5 (P < 0.0001), in the VP and NE groups, respectively. PVR was decreased from 95 ± 34 dyne s/cm5 to 72 ± 30 dyne s/cm5 (P < 0.0001), and from 119 ± 85 dyne s/cm5 to 87 ± 33 dyne s/cm5 (P < 0.0001), respectively. However, PVR/SVR ratio was

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<tr>
<th>Table 1</th>
<th>Demographic data</th>
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<tr>
<td></td>
<td>VP group (n = 25)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>62 ± 6.6</td>
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<tr>
<td>Sex (M/F)</td>
<td>17/8</td>
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<tr>
<td>Weight (kg)</td>
<td>60.8 ± 3.5</td>
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<td>Height (cm)</td>
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Values are mean ± SD. VP: vasopressin; NE: norepinephrine; M/F: male/female. There were no significant differences between the two groups.
increased from 0.09 ± 0.02 to 0.10 ± 0.03 (P = 0.042), and from 0.08 ± 0.03 to 0.09 ± 0.02 (P = 0.041) in the VP and NE groups, respectively (Table 2).

In the NE group, the administration of norepinephrine after milrinone infusion increased MAP from 69 ± 6 mmHg to 89 ± 10 mmHg (P < 0.0001), SVR from 1011 ± 195 dyne s/cm² to 1446 ± 681 dyne s/cm² (P = 0.002), and PVR from 87 ± 33 dyne s/cm² to 139 ± 97 dyne s/cm² (P = 0.043). No significant changes in the PVR/SVR ratio (0.09 ± 0.03 vs 0.09 ± 0.02) and CO were observed (Table 2, Fig. 1).

In the VP group, vasopressin infusion increased MAP from 65 ± 5 mmHg to 78 ± 7 mmHg (P < 0.0001), SVR from 838 ± 209 dyne s/cm² to 1100 ± 244 dyne s/cm² (P < 0.0001), and PVR from 72 ± 30 dyne s/cm² to 84 ± 18 dyne s/cm² (P = 0.042). There was no significant change in the CO. However, the PVR/SVR ratio decreased from 0.10 ± 0.03 to 0.08 ± 0.03 (P = 0.041) (Table 2, Fig. 2), and the changes were significantly different compared to the NE group (0.0188 ± 0.00127 vs 0.000610 ± 0.000481, P < 0.0001) (Fig. 3).

4. Discussion

The main findings of this study are as follows: (1) in anesthetized CABG patients milrinone decreased both SVR and PVR with increased PVR/SVR ratio; (2) both low-dose vasopressin and norepinephrine recovered SVR and PVR which had been reduced by milrinone. However, in contrast to norepinephrine only low-dose vasopressin recovered the PVR/SVR ratio that had been increased by milrinone.

In this study, vasopressin showed selective vasoconstriction on the systemic vessels with a less effect on the pulmonary vessels. Vasopressin has been shown to cause pulmonary vasodilatation in animal studies and this effect was mediated by V1 receptors and endothelium-derived nitric oxide [11,12]. PVR was not increased until a high level of vasopressin concentration was reached (300–500 μg/ml) [13]. However, in the previous clinical studies, the effects of vasopressin were analyzed for systemic blood pressure and SVR [5–7], and PVR or PVR/SVR ratio was rarely reported. Even in a few reports where PVR was measured, the effects of
vasopressin (including its analogue, terlipressin) on pulmonary vessels have not been consistent. Dunser et al. [14] reported the decrease of PAP during the infusion of vasopressin in patients with refractory shock to the catecholamine. Morelli et al. [15] reported the increase of PVR by terlipressin in patients with catecholamine-treated hyperkinetic septic shock.

The possible reasons to explain the variable effects of vasopressin on PVR in clinical studies include: First, vasopressin, when used in low dose, does not affect the blood pressure at normal condition and it acts as a vasopressor only in specific vasodilatory states [15]. Thus, in previous clinical studies [8], vasopressin was infused when the systemic and pulmonary vessels were dilated and it constricted dilated systemic vessels successfully [11]. However, if the pulmonary vessels were fully dilated and there were no further vasodilatory reserve, vasopressin could not dilate them further, even though it has a vasodilatory effect [12,13]. Second, in their studies, patients were already in abnormal hemodynamic states, such as vasodilatory shock or postcardiopulmonary bypass hypotension, when vasopressin infusion was started. As other vasoactive drugs were already being infused, important factors that affect PVR, such as temperature, volume status, and PaCO₂ level could not be controlled.

Phosphodiesterase III inhibitors increase myocardial contractility and can be used in severe heart failure and pulmonary hypertension. However, they may cause vasodilatation and hypotension. Although pulmonary vasodilatation is beneficial for the management of pulmonary hypertension, the decrease of SVR and systemic hypotension may worsen both coronary perfusion and interventricular interaction [16,17], offsetting the beneficial effects of phosphodiesterase III inhibitors especially in the management of pulmonary hypertension and right heart failure. In this study, both norepinephrine and low-dose vasopressin were effective in restoring milrinone-induced decrease of SVR.

In this study, milrinone also increased PVR/SVR ratio, similar to the report by Feneck [18]. However, the increase of PVR/SVR ratio by milrinone was effectively restored only by vasopressin, suggesting vasopressin–milrinone is more suitable than norepinephrine–milrinone in restoring arterial pressure of milrinone-induced hypotension in the management of pulmonary hypertension and right heart failure.

The limitation of our study is that patients may have vascular endothelial dysfunction due to their coronary artery disease. Nevertheless, milrinone–vasopressin combination has theoretical advantages than milrinone–catecholamine combination during CABG. Milrinone improves hemodynamics during the anastomosis of the posterior vessels in patients taking β-blockers [19], and it increases blood flow of grafted internal mammary arteries [20] and middle cerebral arteries [21]. Low-dose vasopressin also selectively dilates the vessels of brain [22] and kidney [23] as well as heart [24]. As these organs are usually the targets of protective strategies, low-dose vasopressin may be more suitable for the management of milrinone-induced hypotension during CABG.

In summary, milrinone decreased both SVR and PVR in anesthetized CABG patients. However, the decrease of SVR was greater than that of PVR, resulting in an increase of PVR/SVR ratio. Although, both norepinephrine and low-dose vasopressin were effective in restoring milrinone-induced decrease of SVR, only low-dose vasopressin decreased the PVR/SVR ratio that was increased by milrinone. Considering the importance of maintaining systemic perfusion pressure as well as reducing right heart afterload, milrinone–vasopressin may provide better hemodynamics than milrinone–norepinephrine during the management of right heart failure.

References


