Effects of milrinone on jugular bulb oxygen saturation and cerebrovascular carbon dioxide reactivity in patients undergoing coronary artery bypass graft surgery

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Background. Jugular bulb oxygen saturation ($S_jVO_2$) is a surrogate marker for global cerebral oxygenation. The effect of milrinone on $S_jVO_2$ and the cerebrovascular carbon dioxide reactivity (CCO2R) was investigated.

Methods. Thirty patients scheduled for coronary artery bypass graft surgery (CABG) were studied prospectively. After sternotomy, normoventilation (at $T_1$; $P_{aCO_2}$=4.7–5.0 kPa) and hyper-ventilation (at $T_2$; $P_{aCO_2}$=3.3–3.7 kPa) were induced and the changes in $S_jVO_2$ ($D_SjVO_2$) and $P_{aCO_2}$ ($D_PaCO_2$), and $D_SjVO_2/D_PaCO_2$ (CCO2R) were measured. After normoventilation was re-established (at $T_3$), milrinone 50 µg kg⁻¹ was given (at $T_4$), followed by hyperventilation (at $T_5$), and $D_SjVO_2$, $D_PaCO_2$ and CCO2R were measured.

Results. After milrinone administration at normoventilation ($T_3$ and $T_4$), cardiac index and mixed venous oxygen saturation increased, while mean arterial pressure and systemic vascular resistance index decreased, without a significant change in $S_jVO_2$. Before milrinone administration ($T_1$ and $T_2$), hyperventilation decreased $P_{aCO_2}$, and $S_jVO_2$, and $D_SjVO_2$ showed positive linear correlation with $D_PaCO_2$. After milrinone administration ($T_4$ and $T_5$), hyperventilation decreased $P_{aCO_2}$ and $S_jVO_2$, and $D_SjVO_2$ showed positive linear correlation with $D_PaCO_2$. There was no significant difference in CCO2R before and after milrinone administration (13.3 (5.7)% kPa⁻¹ and 12.3 (3.9)% kPa⁻¹, respectively).

Conclusions. Although milrinone induced significant haemodynamic changes, $S_jVO_2$ and CCO2R were unchanged during its administration.

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Milrinone is a powerful inodilator which increases the level of cyclic adenosine monophosphate (cAMP) through selective inhibition of the low-$K_m$ cAMP-specific phosphodiesterase (PDE3) in cardiac and vascular smooth muscle.¹² It has been used widely during cardiac surgery and in severe heart failure.¹⁴

Milrinone is known to affect the central nervous system by increasing cerebral blood flow (CBF)⁵–⁸ and preventing chronic cerebral vasospasm after intracranial haemorrhages.⁹¹⁰ However, most previous studies have been performed in animals⁵–⁸ or in patients with a central nervous system deficit.¹¹

The aim of this study was to investigate the effect of milrinone on jugular bulb oxygen saturation ($S_jVO_2$) and the cerebrovascular carbon dioxide reactivity (CCO2R) in patients undergoing coronary artery bypass graft surgery (CABG).

Methods
With the approval of the institutional review board, this prospective study was performed on 30 patients undergoing CABG, with their written consent, between April 2003 and August 2003. Patients known to have clinically significant
preoperative renal or neurological abnormalities, chronic pulmonary disease, a history of carotid artery stenosis or endarterectomy, or severely impaired left ventricular function (ejection fraction <40%) were excluded from the study.

All patients were premedicated with morphine 0.05–0.1 mg kg\(^{-1}\) i.m. Five ECG leads were attached, and leads II and V\(_{5}\) were monitored continuously after the patients arrived in the operating room. A 20-G radial artery catheter was inserted to measure arterial blood pressure and arterial blood gases. A thermodilutional pulmonary artery catheter (Swan-Ganz CCombo/SV\(_{0}\) Model 744HF75, Baxter Healthcare Corporation, Irvine, CA) for monitoring continuous cardiac output (CO) and mixed venous oxygen saturation (SV\(_{0}\)) was inserted in the right internal jugular vein via a 9.0-Fr introducer (AVA HF, Baxter Healthcare Corporation, Irvine, CA). Anaesthesia was induced with midazolam 2.0–3.0 mg, sufentanil 0.2–0.3 \(\mu\)g kg\(^{-1}\) h\(^{-1}\), and rocuronium 50 mg, and maintained with a continuous infusion of sufentanil 0.2–0.3 \(\mu\)g kg\(^{-1}\) h\(^{-1}\), rocuronium 20–30 mg h\(^{-1}\) and inhalation of low-dose isoflurane (under 0.5%) in oxygen (50%) with air. For \(jvO_2\) measurement, an 18-G central venous catheter was inserted into the left internal jugular vein in a cephalad direction via a modified Seldinger technique and, when resistance was sensed, the catheter was withdrawn about 1–2 mm. The positioning of the jugular bulb catheter tip was confirmed radiographically in the operating room. The correct position for the catheter tip was cranial to a line extending from the atlanto-occipital joint space and caudal to the lower margin of the orbit. Samples of jugular bulb blood were drawn at a rate of 1 ml min\(^{-1}\) to reduce the chance of extracerebral blood contamination. After the induction of anaesthesia, the concordance between arterial carbon dioxide pressure (\(P_{\text{ACO}_2}\)) and end-tidal carbon dioxide pressure (\(E_{\text{CO}_2}\)) was measured, and the mechanical ventilation was controlled to maintain normocarbia (\(P_{\text{ACO}_2}=4.7–5.0\) kPa). Arterial oxygen saturation (\(S_{\text{aO}_2}\)), end-expiratory isoflurane concentration (ET-Isop) and nasopharyngeal temperature (Temp) were monitored during the study. The depth of anaesthesia was monitored by a bispectral index score (BIS) monitor (A-200 BIS monitor, Aspect Medical System Inc., Newton, MA). A transoesophageal echocardiographic probe was inserted to monitor ventricular wall motion from the transgastric short-axis view at the mid-papillary level. The operating room temperature was kept above 23\(^\circ\)C, infused fluids were warmed, a warm humidifier was used and a warm air forced blanket was applied during the operation.

After sternotomy, \(P_{\text{ACO}_2}\), arterial oxygen saturation (\(P_{\text{AO}_2}\)), \(jvO_2\), and haemoglobin (Hb) were measured by blood sampling at normocarbia (time \(T_1\)). At the same time, \(S_{\text{aO}_2}\), ET-Isop, BIS, Temp and the haemodynamic variables cardiac index (CI), \(SV_{0}\), mean arterial pressure (MAP) and systemic vascular resistance index (SVRI) were recorded. Thereafter, hyperventilation was induced until \(E_{\text{CO}_2}\) was reduced by about 1.3 kPa from its value at \(T_1\) and maintained for 10 min; the measurements were then repeated (time \(T_2\)).

The difference between \(P_{\text{ACO}_2}\) and \(E_{\text{CO}_2}'\) was re-evaluated and ventilation was adjusted to achieve normocarbia. When the measured \(P_{\text{ACO}_2}\) indicated normocarbia, ventilation was maintained for 10 min and all measurements were repeated (time \(T_3\)). A loading dose of milrinone 50 \(\mu\)g kg\(^{-1}\) was given over 10 min, and it was then continuously infused at 0.5 \(\mu\)g kg\(^{-1}\) min\(^{-1}\) until the end of the study. All the measurements were repeated 20 min after the loading dose of milrinone (time \(T_4\)). Thereafter, hyperventilation was induced until \(E_{\text{CO}_2}\) was reduced by about 1.3 kPa from its value at \(T_4\) and maintained constant for 10 min, and then all the measurements were repeated (time \(T_5\)).

The changes \(\Delta jvO_2\) and \(\Delta P_{\text{ACO}_2}\) were measured between \(T_1\) and \(T_2\), and between \(T_4\) and \(T_5\). Then \(CCO_2R\), expressed as the percentage change in \(jvO_2\), for a 1 kPa change in \(P_{\text{ACO}_2}\) (\(\Delta jvO_2/\Delta P_{\text{ACO}_2}\)), and the correlation between \(\Delta jvO_2\) and \(P_{\text{ACO}_2}\) were calculated.

If MAP decreased below 60 mm Hg at any time during the study, norepinephrine was administered and the patient was excluded. All measurements were performed during harvesting of the internal mammary artery (IMA) and creating the Y-graft between the IMA and the harvested radial artery. Data were analyzed using SPSS version 10.0 (SPSS Inc., Chicago, IL) and expressed as mean (standard deviation). The paired \(t\)-test was used to compare changes between the parameters measured at \(T_1\) and \(T_2\), \(T_2\) and \(T_3\), \(T_3\) and \(T_4\), and \(T_4\) and \(T_5\), and between \(CCO_2R\) values calculated before and after milrinone administration. The bivariate correlation test and the linear regression test were used to analyze the relationship between \(\Delta jvO_2\) and \(\Delta P_{\text{ACO}_2}\). A \(P\)-value <0.05 was considered statistically significant.

**Results**

Patient characteristics are summarized in Table 1. During the study, MAP was maintained above 60 mm Hg in all patients without norepinephrine administration. The mean length of catheter from skin to jugular bulb was 15.5 (SD 0.9, range 13.5–17.0) cm. All patients were discharged from the intensive care unit without any neurobehavioural complications.

During normoventilation, the administration of milrinone significantly increased CI and \(SV_{0}\) (both \(P<0.001\)), and decreased MAP and SVRI (both \(P<0.001\)), but the change in \(jvO_2\) was not significant (\(P=0.58\)) (Table 2).

**Table 1** Patient characteristics (n=30). BSA, body surface area; LVEF, preoperative left ventricular ejection fraction

<table>
<thead>
<tr>
<th>Mean (SD)</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>60.9 (8.2)</td>
</tr>
<tr>
<td>BSA (m(^2))</td>
<td>1.74 (0.16)</td>
</tr>
<tr>
<td>Male:female</td>
<td>19:11</td>
</tr>
<tr>
<td>No. with diabetes mellitus</td>
<td>16</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>59.8 (10.1)</td>
</tr>
</tbody>
</table>
In this study, the effect of milrinone on \(S_jV_02\) and haemodynamic variables during normoventilation. Data are mean (SD), ***P<0.001 compared with the value at \(T_3\), \(P_{ACO2}\) and \(S_jV_02\) at \(T_4\) were not different from the values at \(T_3\) (P=0.78 and P=0.85, respectively).

<table>
<thead>
<tr>
<th>(P_{ACO2}) (kPa)</th>
<th>(S_jV_02) (%)</th>
<th>CI (l min(^{-1}) m(^{-2}))</th>
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<th>MAP (mm Hg)</th>
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<td>At (T_3)</td>
<td>4.7 (0.4)</td>
<td>67.3 (5.9)</td>
<td>2.6 (0.6)</td>
<td>82.3 (4.4)</td>
<td>88.4 (11.0)</td>
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<tr>
<td>At (T_4)</td>
<td>4.8 (0.3)</td>
<td>67.8 (6.5)</td>
<td>3.5 (0.6)</td>
<td>86.8 (3.9)</td>
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**Discussion**

In this study, the effect of milrinone on \(S_jV_02\) and \(CCO2R\). A limitation of \(S_jV_02\) monitoring is that small areas of ischaemia may not be detected. The normal range of \(S_jV_02\) is 60–75%. At \(S_jV_02\) >75% CBF is in excess for CMR. \(S_jV_02\) <50% has been associated with increased cerebral oxygen extraction due to insufficient CBF for CMR, and has been described after traumatic head injury or intracranial surgery\(^{12–14}\) and during the rewarming period of cardiopulmonary bypass (CPB). It has been related to postoperative cognitive decline after cardiac surgery.\(^{17,18}\)

In this study, milrinone increased CI by 33%, decreased SVRI by 35% and MAP by 15%, and significantly increased \(S_jV_02\); however, it did not significantly change \(S_jV_02\) at the same level of \(P_{ACO2}\). There are two possible explanations for the unchanged \(S_jV_02\) after the administration of milrinone. Milrinone may not affect CBF and CMR. Although milrinone induces cerebral artery dilatation and increases CBF in animal studies,\(^{6,7}\) its effect on \(S_jV_02\) in humans with an intact blood–brain barrier (BBB) is unknown. There are several studies of the effects of other PDE inhibitors on CBF. Kruuse and colleagues\(^{19}\) reported that although pentoxifylline, a non-selective PDE inhibitor that increases cAMP, dilated the middle cerebral artery (MCA) and temporal artery, it did not increase regional and global CBF in healthy subjects. Sildenafil, a PDE5 inhibitor that increases cyclic guanosine monophosphate (cGMP), did not increase regional CBF.\(^{20}\) On the other hand, as milrinone is an inodilator producing an increase in CO and vasodilation, it might have proportionally increased both CBF and CMR. Milrinone has been used to reverse cerebral vasospasm following subarachnoid haemorrhage.\(^{9,10}\) Yu and colleagues\(^{21}\) reported that olprinone, another PDE3 inhibitor, increased CO and CBF through its direct vasodilator effect on the cerebral artery in patients with an intact BBB. Some animal studies\(^{6–8}\) suggest that the vasodilatory action of milrinone induces cerebral artery dilation regardless of the integrity of the endothelium. In a human study, the administration of milrinone increased CBF and the blood flow velocity of MCA by 20%, most likely as a result of cerebral vasodilation.\(^{11}\) However, as the blood flow velocity of MCA was measured with transcranial Doppler ultrasonography, which does not directly measure the quantitative change in CBF, the effect of milrinone on CBF is unclear. Although milrinone preserved the coupling between CBF and CMR, its separate effects on CBF and CMR were not clarified in this study and further investigation is needed.

\(CCO2R\) is a marker of the ability of the cerebral vasculature to respond to cerebral metabolic demands. Normally independent of perfusion pressure, \(CCO2R\) is influenced by the cerebrovascular resistance (CVR),\(^{22,23}\) decreasing as CVR increases. It is known that carbon dioxide freely diffuses across the blood–brain barrier and that changes in \(P_{ACO2}\) have a positive linear correlation with the changes in CBF, without affecting CMR, under both awake and anaesthetized conditions.\(^{24,25}\) In this study, \(\Delta S_jV_02\) showed a significant positive linear correlation with \(\Delta P_{ACO2}\) and \(CCO2R\) was unchanged after milrinone administration.

**Table 2** The effect of milrinone on \(S_jV_02\) and haemodynamic variables during normoventilation. Data are mean (SD), ***P<0.001 compared with the value at \(T_3\), \(P_{ACO2}\) and \(S_jV_02\) at \(T_4\) were not different from the values at \(T_3\) (P=0.78 and P=0.85, respectively).

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Therefore it is suggested that milrinone preserves CCO₂R. In particular, since \( S_jV_O \) decreased to 53.6% when \( P_{ACO_2} \) decreased to 3.6 kPa, careful monitoring and maintenance of the \( P_{ACO_2} \) level within the normocarbia range is necessary during milrinone administration to prevent cerebral hypoperfusion, regardless of the changes in haemodynamics.

In this study, MAP decreased by a mean of 13 mm Hg after milrinone administration but was maintained above 60 mm Hg, thus preserving pressure-flow cerebral autoregulation.\(^{25}\) Since other variables that affect \( S_jV_O \), such as \( P_{AO_2}, S_aO_2, Hb, ET-Isof \) and Temp, were constant throughout the study, they would not have affected the result. In this study, high-dose sufentanil and isoflurane <0.4% were used for anaesthesia. It is known that high-dose sufentanil preserves not only the coupling between CBF and CMR, but also CCO₂R.\(^{26,27}\) Although all inhalation anaesthetics above 1.0 MAC, including isoflurane, are known to impair the coupling between CBF and CMR, the dose of isoflurane used in this study is known to have a relatively small effect on the coupling between CBF and CMR.\(^{28,29}\) The BIS value, indicating the degree of anaesthetic depth, was kept between 50 and 60 during this study. Patients with neurological abnormalities, a history of carotid artery stenosis or severely impaired left ventricular function were excluded. Further studies are needed to investigate the effect of milrinone on \( S_jV_O \) and CCO₂R in these patients.

In conclusion, although milrinone induced significant haemodynamic changes, \( S_jV_O \) and CCO₂R were unchanged. Consequently, maintenance of \( P_{ACO_2} \) within the normal range is important to prevent cerebral hypoperfusion.

References


