Milrinone decreases both pulmonary arterial and venous resistances in the hypoxic dog

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Summary

We have studied the effect of milrinone on pulmonary vascular resistance (PVR) in dogs with hypoxic pulmonary vasoconstriction (HPV). Using a pulmonary arterial occlusion method, we measured effective pulmonary capillary pressure (Pcap) by which total PVR was partitioned into arterial (PVRa) and venous (PVRv) components. Hypoxic ventilation (FiO2 = 0.11–0.13) produced significant increases in mean pulmonary arterial pressure (PAP) and Pcap (P < 0.01) associated with increases in PVRa and PVRv (P < 0.01). During the hypoxic period, milrinone significantly decreased mean PAP and Pcap (P < 0.01), reflected in decreases in PVRa and PVRv (P < 0.01). The longitudinal distribution of PVR (PVRa/PVRv) remained unchanged throughout the experiment, indicating that HPV occurred equally in the arterial and venous segments and that milrinone-induced vasodilatation occurred equally in both segments. During hypoxia, milrinone did not produce an increase in cardiac output or a decrease in PAO2. Milrinone also produced significant decreases in mean systemic arterial pressure (P < 0.01) and systemic vascular resistance (P < 0.05) to a similar extent to the decreases in mean PAP and PVR, suggesting no selective dilating effect of milrinone on the pulmonary vasculature. These results indicate that in HPV, milrinone decreased the vascular tone of both pulmonary arterial and venous segments without increasing cardiac work or impairing pulmonary oxygenation. This suggests a potential for use in patients suffering from hypoxic pulmonary hypertension. (Br. J. Anaesth. 1998; 81: 920–924).

Keywords: pharmacology, milrinone; cardiorespiratory system, effects; lung, intravascular pressures; hypoxia; lung, vasculature; dog

Hypoxic pulmonary vasoconstriction (HPV) plays an important role in inducing pulmonary hypertension in several acute and chronic lung diseases, including the acute respiratory distress syndrome (ARDS), pulmonary oedema, pulmonary embolism, chronic obstructive airways disease and pulmonary fibrosis.1 Although HPV is a physiological adaptation to alveolar hypoxia,2 associated pulmonary hypertension may produce adverse effects, particularly in patients suffering from cardiovascular dysfunction.3–4 Milrinone, a phosphodiesterase III inhibitor, is used to improve pulmonary haemodynamics in association with systemic haemodynamic dysfunction.3–5 Several workers have advocated the preferential effect of milrinone on pulmonary haemodynamics over systemic haemodynamics in pulmonary hypertension.3–4 However, to our knowledge no study has focused on the effect of milrinone on pulmonary hypertension produced by HPV or the effector site of milrinone in the pulmonary vascular tree.

Therefore, the aims of this study were to examine if milrinone improves pulmonary haemodynamics in acute HPV and, if it does, to explore if milrinone produces differential vasodilating effects in the pulmonary vascular tree. To assess the longitudinal distribution of pulmonary vascular resistance (PVR), we used a pulmonary arterial occlusion technique.5–9 This technique estimates effective pulmonary capillary pressure (Pcap) by which PVR is partitioned into arterial and venous components.

Materials and methods

This study was approved by the Animal Welfare Committee, Laboratory Animal Centre, School of Medicine, Chiba University.

ANIMAL PREPARATION

We studied seven healthy mongrel dogs (aged 3–5 yr, weight 12–20 kg (mean 16.7 kg) premedicated with ketamine 10 mg kg−1 i.m. Anaesthesia was induced by pentobarbitals, 20–40 mg kg−1 i.v. and maintained by continuous infusion of pentobarbitals (pentobarbitone) 5–10 mg kg−1 h−1. The dogs were paralysed with pancuronium 0.1 mg kg−1 at hourly intervals, the trachea intubated and the lungs ventilated mechanically with 30–40% oxygen in nitrogen. Respired gas was sampled continuously at the proximal end of the tracheal tube to monitor inspired oxygen and end-tidal carbon dioxide tensions (Anaesthetic Gas Monitor Type 1304, Brue & Kjaer, Copenhagen, Denmark). Mechanical ventilation was adjusted to maintain end-tidal carbon dioxide partial pressure at 4.0–5.3 kPa. Lactate Ringer’s solution 6 ml kg−1 h−1 i.v. was administered for maintenance fluid replacement. The surface ECG (lead II) was monitored with skin needle electrodes. Rectal temperature was maintained at approximately 37°C using an overhead heating lamp.
**Effects of milrinone on HPV**

HAEMODYNAMIC MEASUREMENTS

We measured systemic arterial pressure (SAP) continuously via a catheter inserted into the right femoral artery (L989–39, Abbott Critical Care Systems, Tokyo, Japan and 78534A Hewlett Packard, Silicon Valley, CA, USA). Pulmonary arterial pressure (PAP) was measured via a 5-French gauge pulmonary artery catheter (Arrow, Reading, PA, USA) inserted into the pulmonary artery via the right femoral vein. Central venous pressure (CVP) was measured via the side port of the pulmonary artery catheter at 3-min intervals. Continuous measurement of cardiac output (CO) was performed using an 8-French gauge catheter inserted into the pulmonary artery from the left femoral vein and connected to a thermodilution CO monitor (Intelicath and Vigilance, Baxter Healthcare, Irvine, CA, USA).

All haemodynamic data were stored on personal computer for offline analysis.

EXPERIMENTAL SEQUENCE

We started haemodynamic measurements after obtaining stable circulatory conditions after recovery from the surgical procedure and instrumentation. Our experimental sequence consisted of four phases of 30 min duration each: (1) control, (2) hypoxia (HYPO), (3) hypoxia + milrinone (H-M) and (4) milrinone (MIL). After control measurements at 3-min intervals during mechanical ventilation with 30–40% oxygen in nitrogen and measurements were repeated at 3-min intervals (HYPO). After a 30-min HYPO phase, a loading dose of milrinone 60 mg kg\(^{-1}\) was given followed by continuous infusion of 6 mg kg\(^{-1}\) h\(^{-1}\) was started and all the measurements were repeated (H-M). This milrinone regimen has been reported to produce therapeutic plasma concentrations for treatment of left ventricular dysfunction in humans. Finally, \(P_{\text{cap}}\) was restored to control values and measurements were performed every 3 min (MIL).

Each measurement included determination of CO and CVP values, together with 25-s data sampling of SAP and PAP.

PULMONARY ARTERIAL OCCLUSION TECHNIQUE AND CALCULATION OF PULMONARY AND SYSTEMIC HAEMODYNAMICS

We used a pulmonary artery occlusion technique for the intact lung preparation developed by Hakim and colleagues to estimate \(P_{\text{cap}}\). At end-expiration, mechanical ventilation was stopped and 25-s data sampling started. Ten seconds after the start of data sampling, pulmonary arterial occlusion for 15 s was performed by inflating the pulmonary artery catheter balloon instantaneously. This technique estimates \(P_{\text{cap}}\) from the pressure decay curve after pulmonary artery occlusion. The theory of the occlusion method is presented in figure 1. \(P_{\text{cap}}\) was noted as the pressure at the point where the monoexponential fitting curve merged with the measured pressure decay curve. More commonly used is the method which estimates \(P_{\text{cap}}\) by extrapolating the fitting curve to the instant of occlusion. However, we adopted the merging method as the instant of occlusion could not be identified precisely because of relatively slow inflation of the catheter balloon compared with rapidly responding occluders such as solenoid valves.

It has been reported that in various pulmonary haemodynamic conditions, although the merging point method underestimated \(P_{\text{cap}}\) slightly, the difference between the estimated and "true" \(P_{\text{cap}}\) was within the range of experimental and computational errors and the estimated \(P_{\text{cap}}\) was able to track the changes in "true" \(P_{\text{cap}}\). Pulmonary microvascular pressure is known to be pulsatile, indicating that the estimated \(P_{\text{cap}}\) varies according to the point in the cardiac cycle at which the pulmonary artery is occluded. Therefore, the mean of the two measurements obtained from occlusions at the systolic and diastolic phases was termed \(P_{\text{cap}}\). Pulmonary arterial wedge pressure (PAWP) was obtained as the mean pressure at 10–11 s after occlusion.

Mean SAP (mSAP) and mean PAP (mPAP) were computed respectively from 8–10 heartbeats immediately before pulmonary arterial occlusion. Several studies showed that the CO measurement system used in this study exhibited a delayed time response when subjects exhibited unstable haemodynamics. Therefore, we corrected CO for the delayed response time by applying a correction function obtained from published data. Systemic vascular resistance (SVR) was defined as (mSAP–CVP)/CO.

Partitioning pulmonary vascular pressure gradient into pre- (arterial) and post-capillary (venous) components by \(P_{\text{cap}}\), pulmonary arterial (PVRa) and venous (PVRv) resistances were defined as (mPAP–\(P_{\text{cap}}\))/CO and (\(P_{\text{cap}}\)–PAWP)/CO, respectively. Thus total PVR (PVRTot) = PVRa + PVRv. Longitudinal distribution of PVR was defined as PVRv/PVRa.

BLOOD–GAS SAMPLING

Arterial and mixed venous blood-gas analyses were...
performed (Model 170 pH/Blood Gas Analyser, Ciba-Corning, Tokyo, Japan) every 20 min in each phase.

**STATISTICAL ANALYSIS**

Data were analysed by repeated measures analysis of variance followed by Student–Newman–Keuls test. \( P<0.05 \) was considered significant.

**Results**

Blood-gas data are shown in table 1. Both arterial pH and \( P_{\text{A CO}_2} \) were within the physiological range throughout all phases. \( P_{\text{A O}_2} \) decreased significantly during hypoxic ventilation but milrinone did not produce further changes in \( P_{\text{A O}_2} \) (H-M vs HYPO). There was a similar trend in mixed venous oxygen tension (\( P_{\text{V O}_2} \)) to that of \( P_{\text{A O}_2} \). Systemic haemodynamic data are shown in table 2. Hypoxia (HYPO) produced approximately 10% increases (\( P<0.05 \)) in CO compared with control, and milrinone did not produce a further increase in CO (H-M and MIL). mSAP and SVR decreased significantly during administration of milrinone (H-M and MIL).

Figure 2 illustrates the changes in pulmonary haemodynamics. Both mPAP and Pcap increased significantly during HYPO compared with control (\( P<0.01 \)) (fig. 2A). H-M produced significant decreases in mPAP, Pcap and PAWP compared with HYPO (\( P<0.01 \)). HYPO produced significant increases in both PVRa and PVRv from control (\( P<0.01 \)) (fig. 2B). Administration of milrinone (H-M) produced significant reductions in PVRtot, PVRa and PVRv which were increased during HYPO (\( P<0.05 \)). After reversal of hypoxia (MIL), all pulmonary haemodynamic variables returned to control values. PVRv/PVRa remained unchanged throughout all phases (fig. 2C).

Figure 3 illustrates serial changes in PVR and its longitudinal distribution. Induction of hypoxia (HYPO) produced initial rapid increases in all three resistances (PVRtot, PVRa and PVRv), followed by further gradual increases. Milrinone produced a rapid reduction in the increased resistances, followed by a gradual reduction (H-M). PVRv/PVRa did not change throughout the four phases.

**Table 1** Blood-gas data (mean (SEM), \( n=7 \) dogs). **\( P<0.01 \) compared with both control and HYPO; †† \( P<0.01 \) compared with both control and MIL.

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>HYPO</th>
<th>H-M</th>
<th>MIL</th>
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<tbody>
<tr>
<td>pH</td>
<td>7.39 (0.02)</td>
<td>7.41 (0.01)</td>
<td>7.38 (0.01)</td>
<td>7.36 (0.02) **</td>
</tr>
<tr>
<td>( P_{\text{A CO}_2} ) (kPa)</td>
<td>4.7 (0.3)</td>
<td>4.7 (0.3)</td>
<td>4.9 (0.3)</td>
<td>5.1 (0.3)</td>
</tr>
<tr>
<td>( P_{\text{A O}_2} ) (kPa)</td>
<td>17.9 (2.4)</td>
<td>6.0 (0.5) ††</td>
<td>5.9 (0.4) ††</td>
<td>20.0 (2.7)</td>
</tr>
<tr>
<td>( P_{\text{V O}_2} ) (kPa)</td>
<td>6.7 (0.4)</td>
<td>4.7 (0.4) ††</td>
<td>4.7 (0.4) ††</td>
<td>7.3 (0.3)</td>
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</table>

**Table 2** Systemic haemodynamic data (mean (SEM), \( n=7 \) dogs). † \( P<0.05 \), †† \( P<0.01 \) compared with control; * \( P<0.05 \), ** \( P<0.01 \) compared with HYPO.

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>HYPO</th>
<th>H-M</th>
<th>MIL</th>
</tr>
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<tbody>
<tr>
<td>CO (litre min (^{-1}))</td>
<td>2.4 (0.3)</td>
<td>2.7 (0.5) †</td>
<td>2.6 (0.3) †</td>
<td>2.4 (0.2)</td>
</tr>
<tr>
<td>mSAP (mm Hg)</td>
<td>121 (8)</td>
<td>131 (5) ††</td>
<td>105 (7) †**</td>
<td>95 (2) ††**</td>
</tr>
<tr>
<td>SVR (mm Hg litre (^{-1}) min)</td>
<td>52 (8)</td>
<td>55 (7)</td>
<td>39 (3) †*</td>
<td>38 (3) †*</td>
</tr>
</tbody>
</table>
Discussion

Before discussing the implications of our results, we should consider what Pcap, estimated by our occlusion method, represents. Partitioning of PVR into arterial and venous segments by estimated Pcap depends on the theoretical model adopted for interpretation of the pulmonary arterial pressure decay curve after occlusion, and does not necessarily correlate precisely with anatomical structure. It is possible that the functional venous (post-capillary) segment defined by our method may include some anatomically arterial vessels in the pulmonary capillary segment, and vice versa. Thus it is important to note that the segments functionally partitioned by the occlusion method can only approximate to the mechanical characteristics of their anatomical correlates. With other reasons, such as experimental design and analytical methods, this functional and anatomical discordance could be an explanation for the wide range of longitudinal distribution of PVR reported in other studies, such as −0.3–1.2 of PVRa/PVRv during hypoxia and normoxia.12–16 Our results of 0.37 and 0.39 for PVRa/PVRv at control and HYPO, respectively, are at the lower end of the range of values reported by previous studies.

There are discrepancies as to the site of HPV, probably arising from differences in lung preparation, species, degree of hypoxia and measurement technique (occlusion device and adopted theoretical model). It has been reported that small arteries residing in the pre-capillary segment are the main site of vasoconstriction in response to alveolar hypoxia.12–14 In contrast, recently published studies have indicated a significant contribution of the post-capillary venous segment in addition to the pre-capillary segment to the increase in PVR during alveolar hypoxia.15 16 Hillier and colleagues demonstrated that alveolar hypoxia of a similar degree to that reported in this study produced active constriction of both arterioles and venules, even though these vessels lack obvious smooth muscle structure.17 Contraction of the capillary arterioles and venules would result in increases in PVRa and PVRv, respectively, if our occlusion technique was used. Our finding that both PVRa and PVRv increased by the same magnitude is consistent with these studies.

The mechanism of the decrease in PVR produced by milrinone cannot be determined from our results. Passive pulmonary vasodilatation is induced by increased blood flow or increased distending pressure, or both.18–19 In our case, however, this passive mechanism is unlikely as milrinone produced no significant change in CO and a 30% decrease in mPAP. Possible mechanisms might include direct relaxation of pulmonary vessels and recruitment of pulmonary vessels20–21 associated with inter-regional redistribution of blood flow.

Some pulmonary vasodilators such as prostacyclin, prostaglandin E1, and nitroglycerine are known to decrease PVRa and PVRv.22–24 Alveolar hypoxia in the whole lung induces capillary recruitment and intrapulmonary blood flow redistribution towards well-ventilated lobes in an attempt to minimize the deterioration in pulmonary oxygenation.2 25 Pulmonary vasodilatation produced by vasodilators hampers this adaptation process, resulting in increases in Qs/Qt and worsened pulmonary oxygenation.20–23 24 In our study, milrinone did not worsen pulmonary oxygenation from the initial hypoxia. As milrinone did not change CO or P\textsubscript{50\%,} it might not increase Qs/Qt. The reason why milrinone did not cause further deterioration in pulmonary oxygenation is not obvious from our results. However, the dose used in our study might have been relatively small and insufficient to increase cardiac output, which would have led to deleterious redistribution of pulmonary blood flow, but was still sufficient to produce pulmonary vasodilatation. This differential effect might be caused in part by the nitric oxide-like effect of milrinone.26 Another possibility is that the decrease in capillary pressure reduced hyperaemia of the area where gas exchange was occurring, leading to improvement in gas exchange.27 This would cancel out the ventilation–perfusion mismatching which would have been produced by milrinone-induced vasodilatation.

Reduction of PVR by milrinone may be beneficial in patients suffering from diseases characterized by increased Pcap with HPV, such as ARDS. These patients are susceptible to pulmonary oedema by pulmonary flow distribution imbalance28 and the reduction of elevated Pcap by milrinone may therefore decrease the chance of pulmonary oedema.9 Absence of selective vasodilatation of the pulmonary vasculature by milrinone in our study may suggest that it has no potential use in the development of pulmonary hypertension induced by HPV. However, our finding that milrinone reduced PVR with no increase in CO implies that milrinone may reduce right heart afterload without itself increasing cardiac work. Therefore, with a synergistic effect on systemic haemodynamics, milrinone might be of use in the treatment of pulmonary hypertension in patients with systemic cardiovascular disorders, in particular, right heart dysfunction.

References


